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American Journal of OBSTETRICS AND GYNECOLOGY

Transactions of the Eightieth Annual Meeting of the American Gynecological Society

Editors

HOWARD C. TAYLOR, JR. WILLIAM J. DIECKMANN

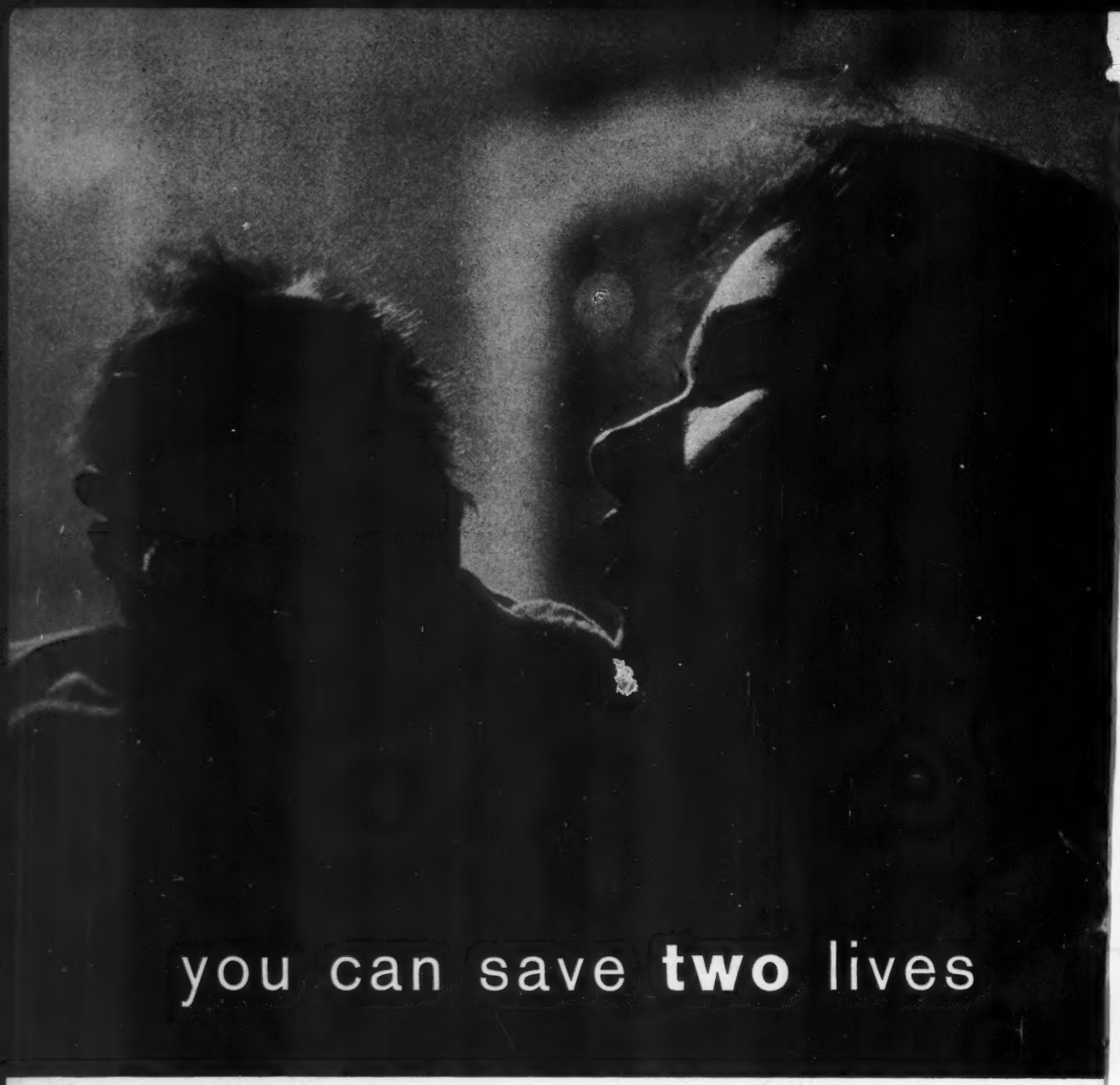
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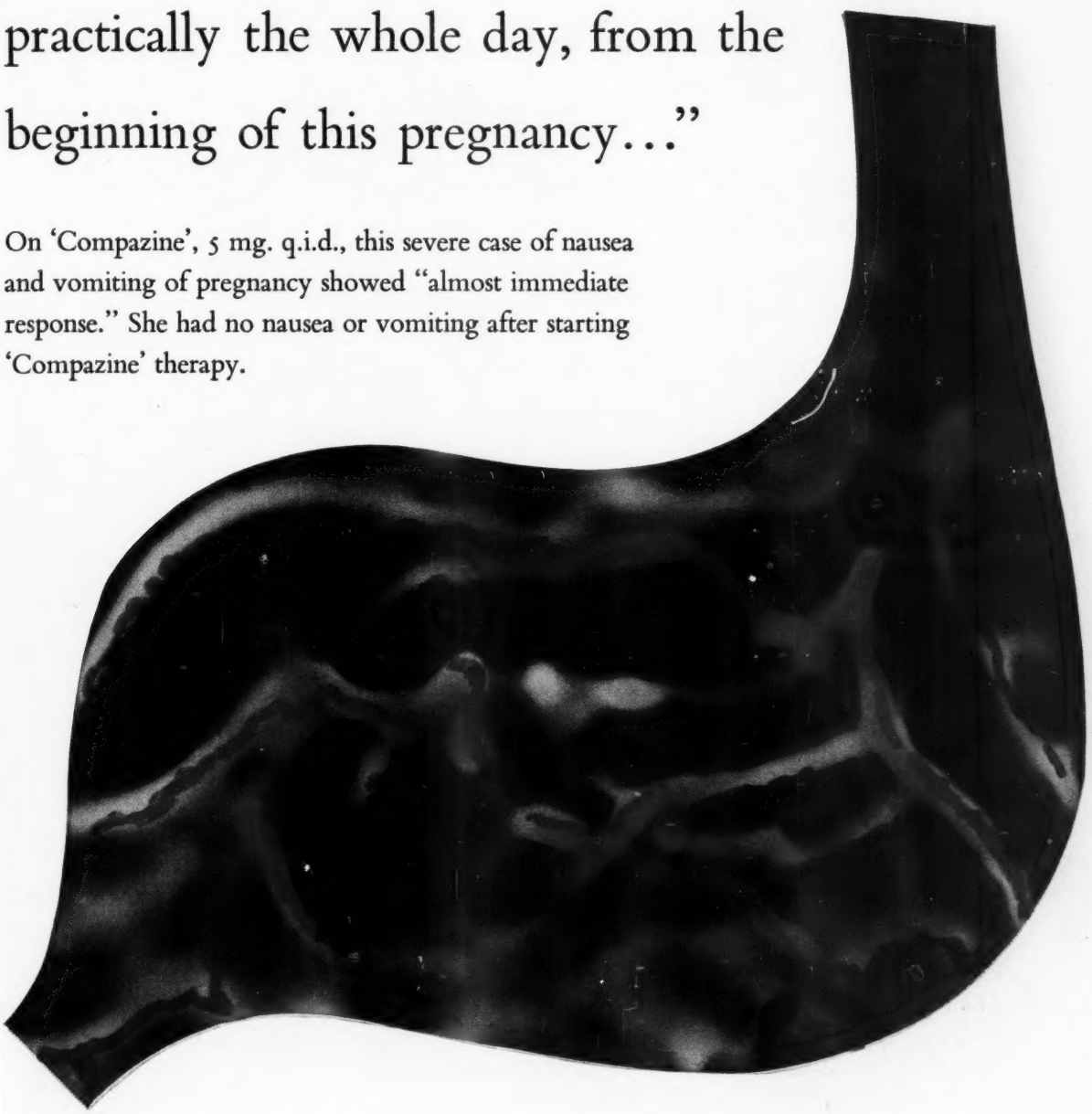
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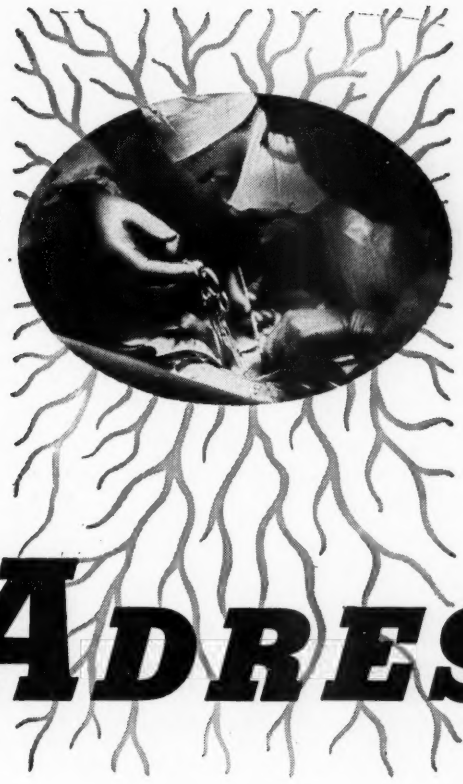
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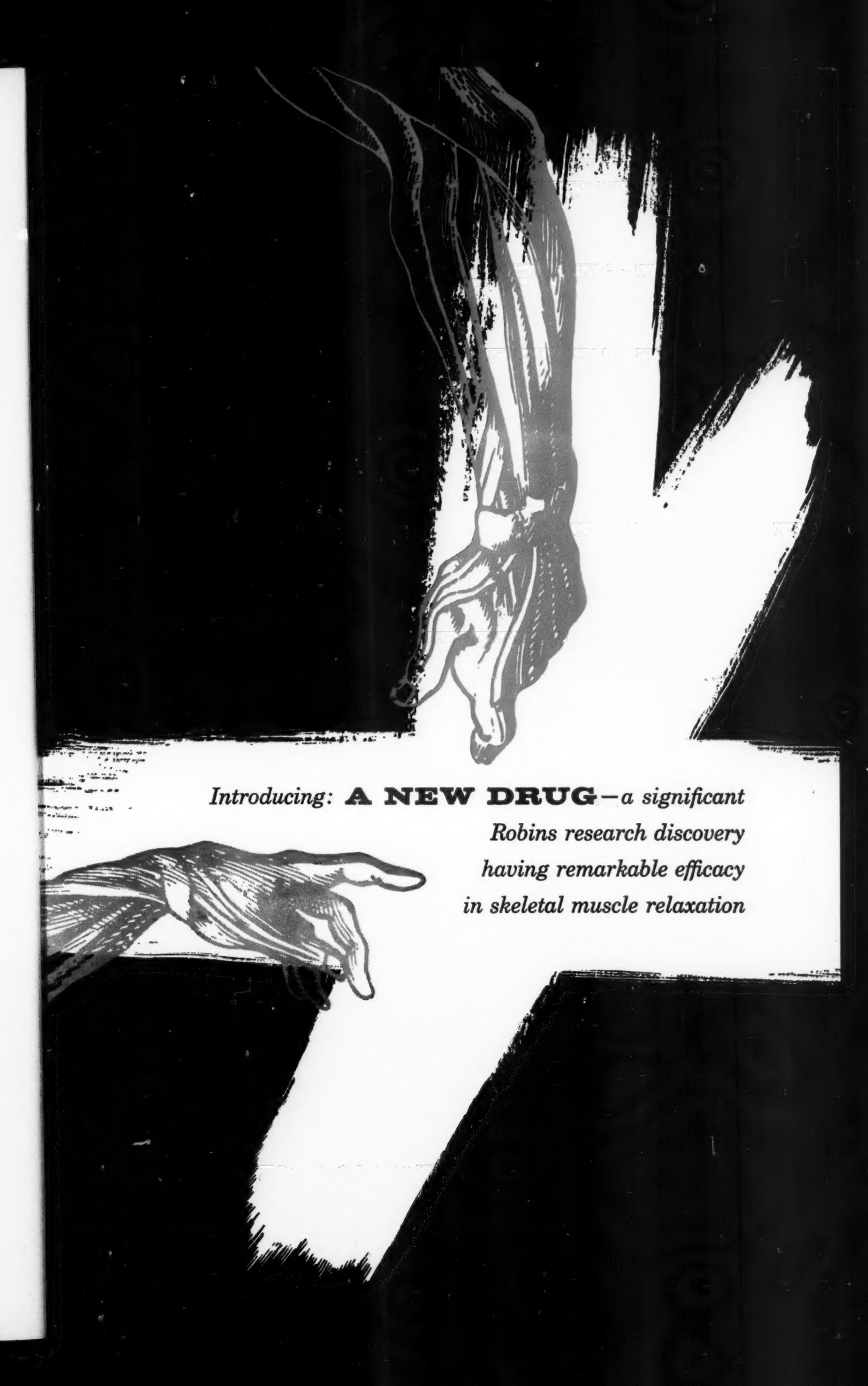
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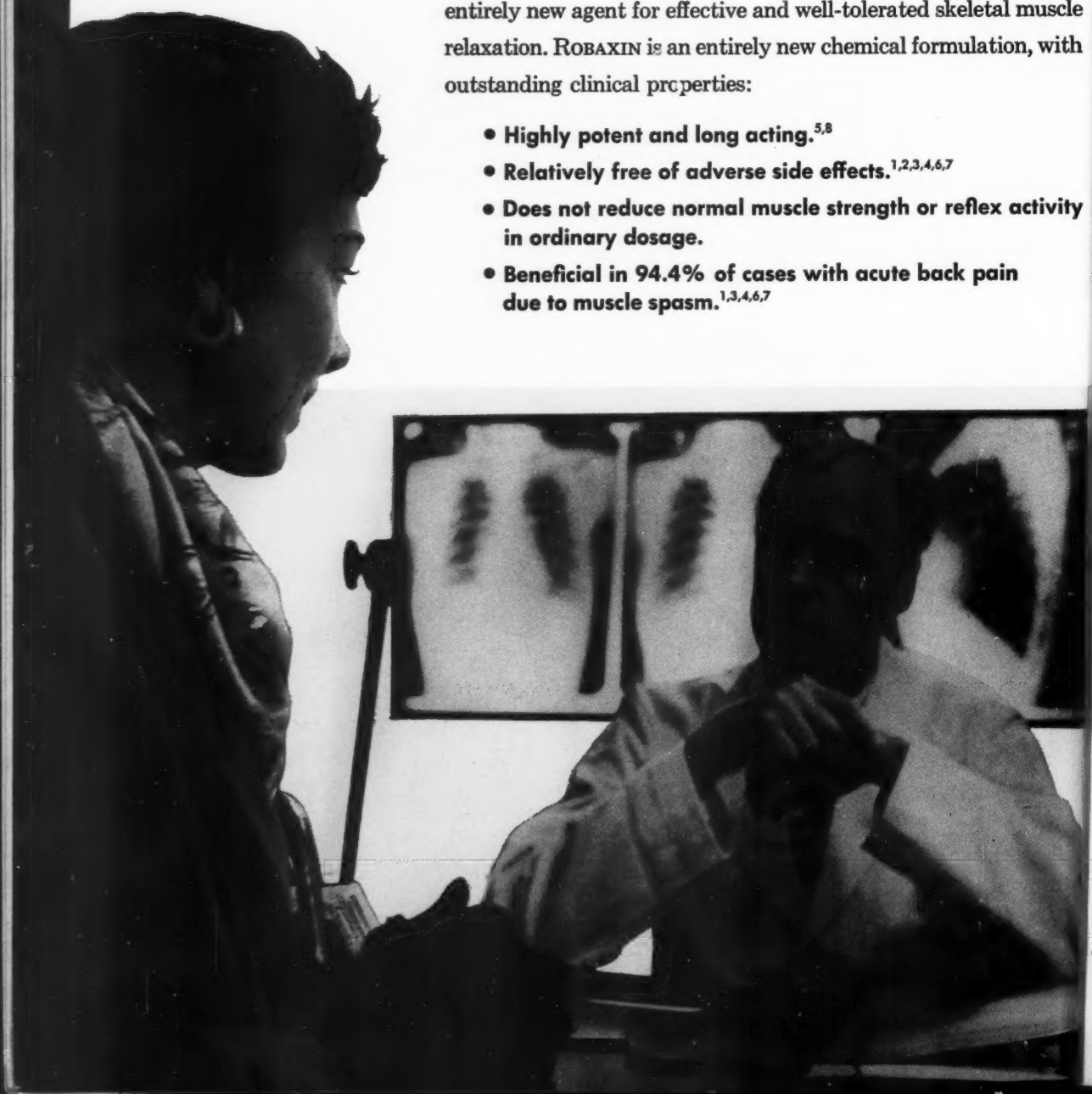
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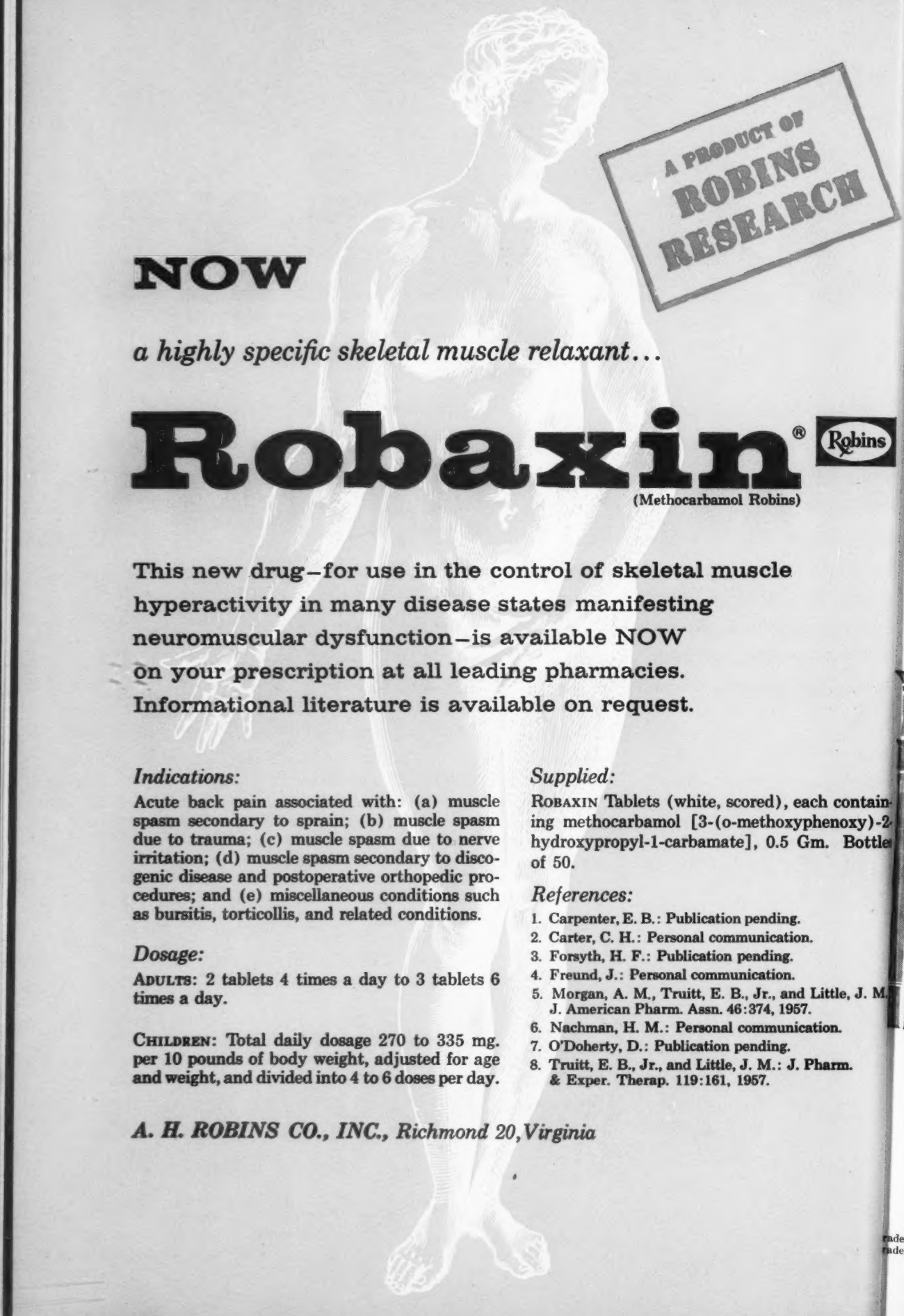
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Acute back pain due to								
(a) Muscle spasm secondary to sprain	18	2-42 days	3-6 Gm.	17	1	0	0	None, 16; Dizziness, 1; Slight nausea, 1.
(b) Muscle spasm due to trauma	13	1-42 days	2-6 Gm.	8	1	3	1	None, 12; Nervousness, 1.
(c) Muscle spasm due to nerve irritation	5	4-240 days	2.25-6 Gm	4	1	0	0	None, 5.
(d) Muscle spasm secondary to discogenic disease and postoperative orthopedic procedures	30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25; Dizziness, 1; Lightheadedness, 2 Nausea, 2.*
Miscellaneous (bursitis, torticollis, etc.)	6	3-60 days	4-8 Gm.	6	0	0	0	None, 6.
TOTAL	72			59	6	3	4	

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References:

1. Carpenter, E. B.: Publication pending.
2. Carter, C. H.: Personal communication.
3. Forsyth, H. F.: Publication pending.
4. Freund, J.: Personal communication.
5. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: J. American Pharm. Assn. 46:374, 1957.
6. Nachman, H. M.: Personal communication.
7. O'Doherty, D.: Publication pending.
8. Truitt, E. B., Jr., and Little, J. M.: J. Pharm. & Exper. Therap. 119:161, 1957.

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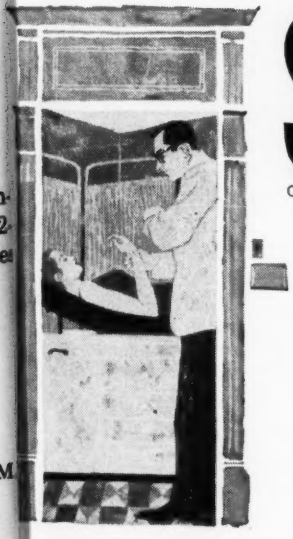




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1. *Pennington, V. M.: Meprobamate (Miltown) in premenstrual tension. J.A.M.A.* **164**:*638, June 8, 1957.*

2. *Selling, L. S.: Clinical study of a new tranquilizing drug: use of Miltown (2-methyl-2-n-propyl-1,3-propanediol dicarbamate). J.A.M.A.* **157**:*1594, April 30, 1955.*

3. *Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gyn.* **9**:*703, June 1957.*

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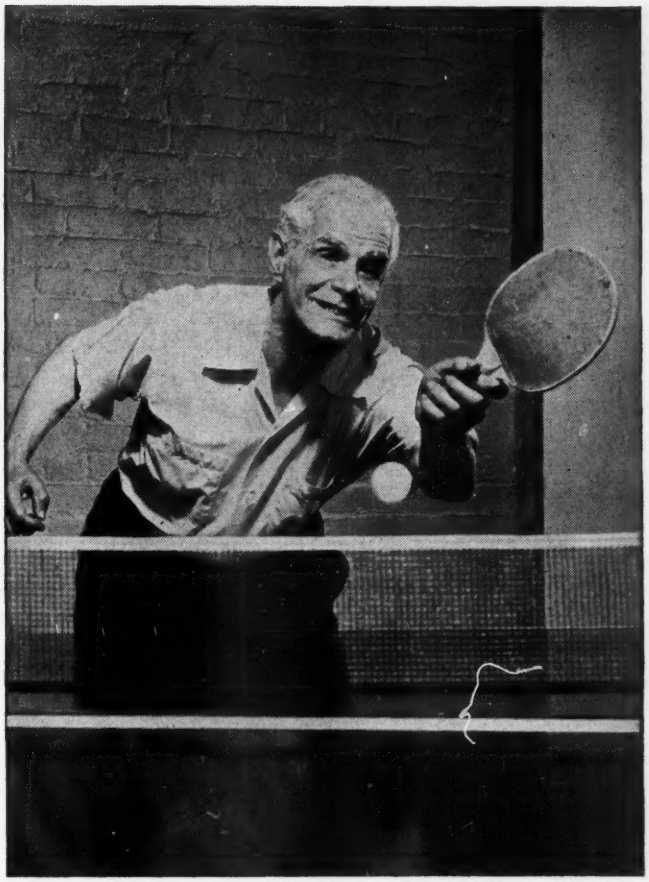


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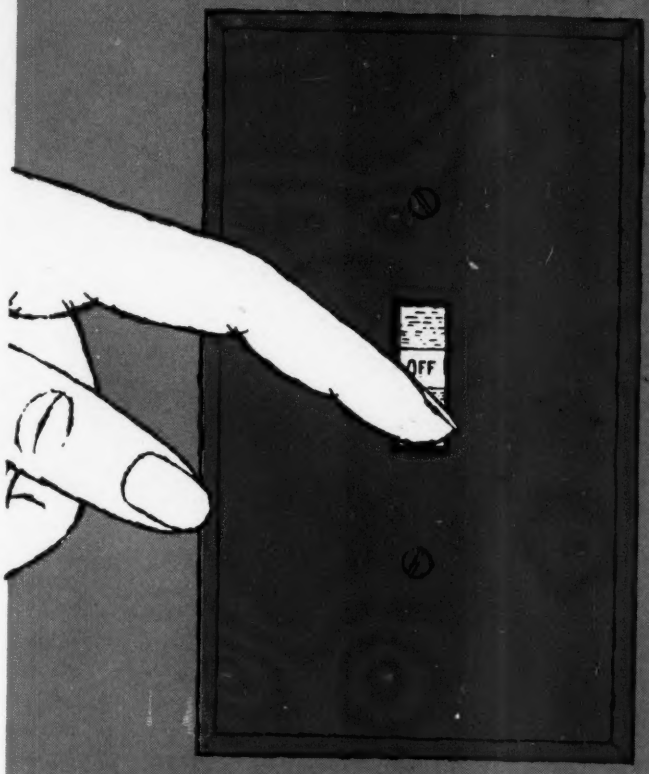
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REFERENCES

(1) Chan, Y. T. and Hays, E. E., The American Journal of the Medical Sciences, August 1957; (2) Townsend, E. H., Jr., In Press; (3) Weismiller, F., In Press; (4) Cass, Leo J. and Frederik, W. S., In Press.



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in monilial vaginitis –
"... more effective than any other agent ... used previously."[2]



in mixed infection –
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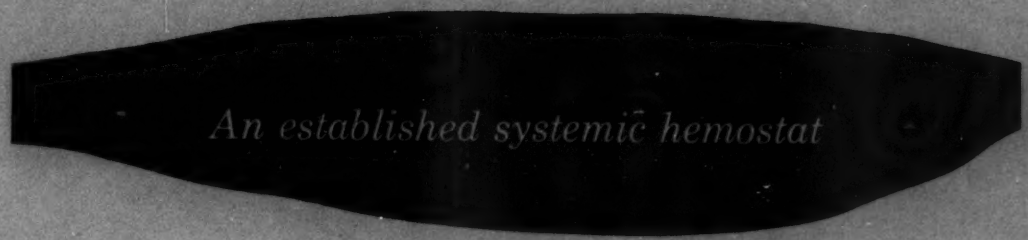
Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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1. Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. 6:617 (June, 1953).



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References: 1. Woodhull, R. B.: Obst. & Gynec. 3:201, 1954. 2. Ausman, D. C.: Wisc. M. J. 53:322, 1954. 3. Edwards, B. E.: J. Indiana M. A. 47:869, 1954. 4. Ivory, H. S.: J. M. Soc. New Jersey 51:273, 1954.

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1. Amer. J. Obst. & Gynec., 68:1321, 1954.



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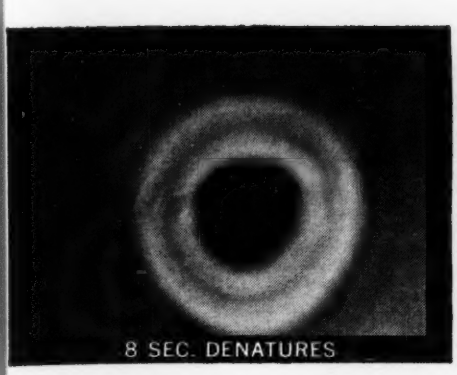
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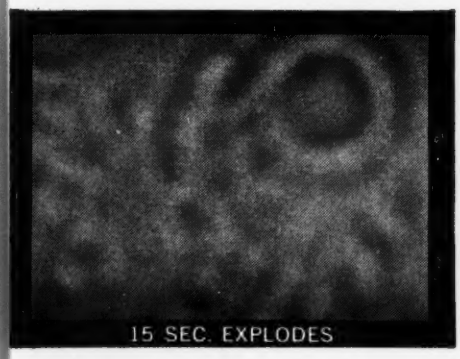
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VAGISEC liquid and jelly, used by the Davis technique,† offer a new approach to successful treatment of vaginal trichomoniasis.[1-4] By *exploding* — not merely inactivating — hard-to-reach flagellates as well as those in surface secretions, VAGISEC therapy quickly rids the vagina of trichomonads that tend to survive and cause flare-ups.*

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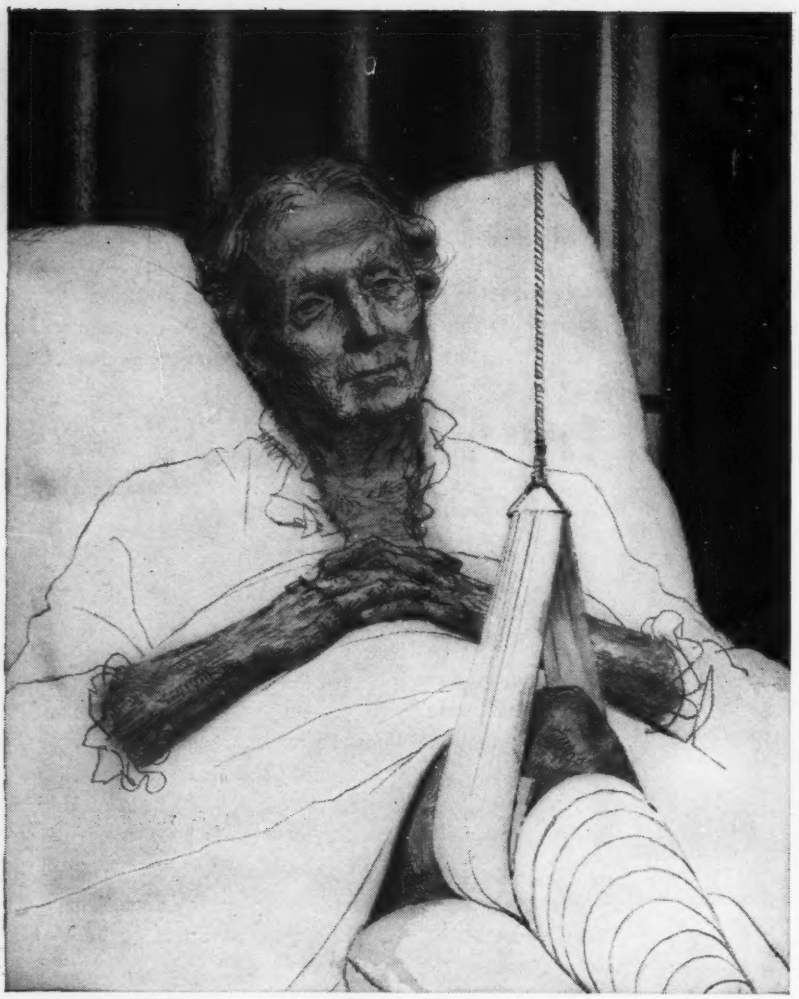
REFERENCES:

1. Decker, A.: New York J. Med. *57*:2237 (July 1) 1957.
2. McGoogan, L. S.: J. Michigan M. Soc. *55*:682 (June) 1956.
3. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, W. F. Prior, 1955, vol. 3.
4. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955.
5. Draper, J. W.: Internat. Rec. Med. *168*:563 (Sept.) 1955.
6. Karnaky, K. J.: J.A.M.A. *155*:876 (June 26) 1954.
7. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations, and Discharges, New York, The Blakiston Co., 1953.

*For a small percentage of women who have an involvement of cervical, vestibular or urethral glands, additional measures are required.[1,3,4]

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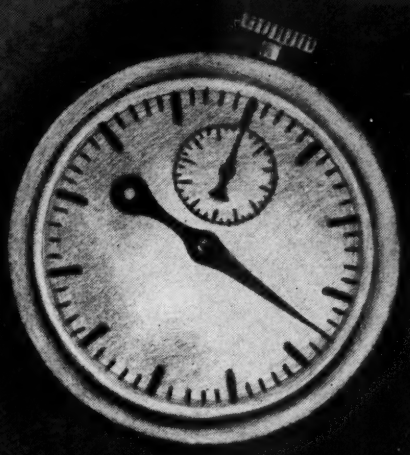
*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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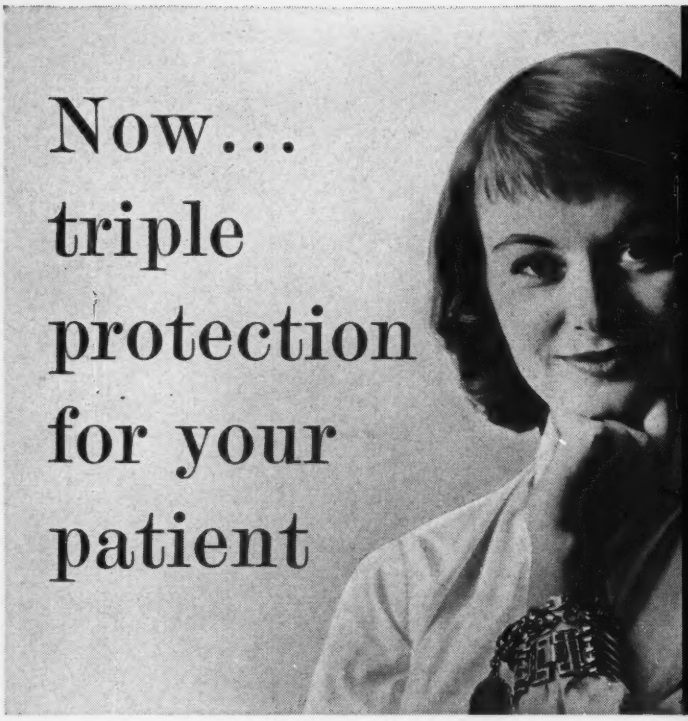
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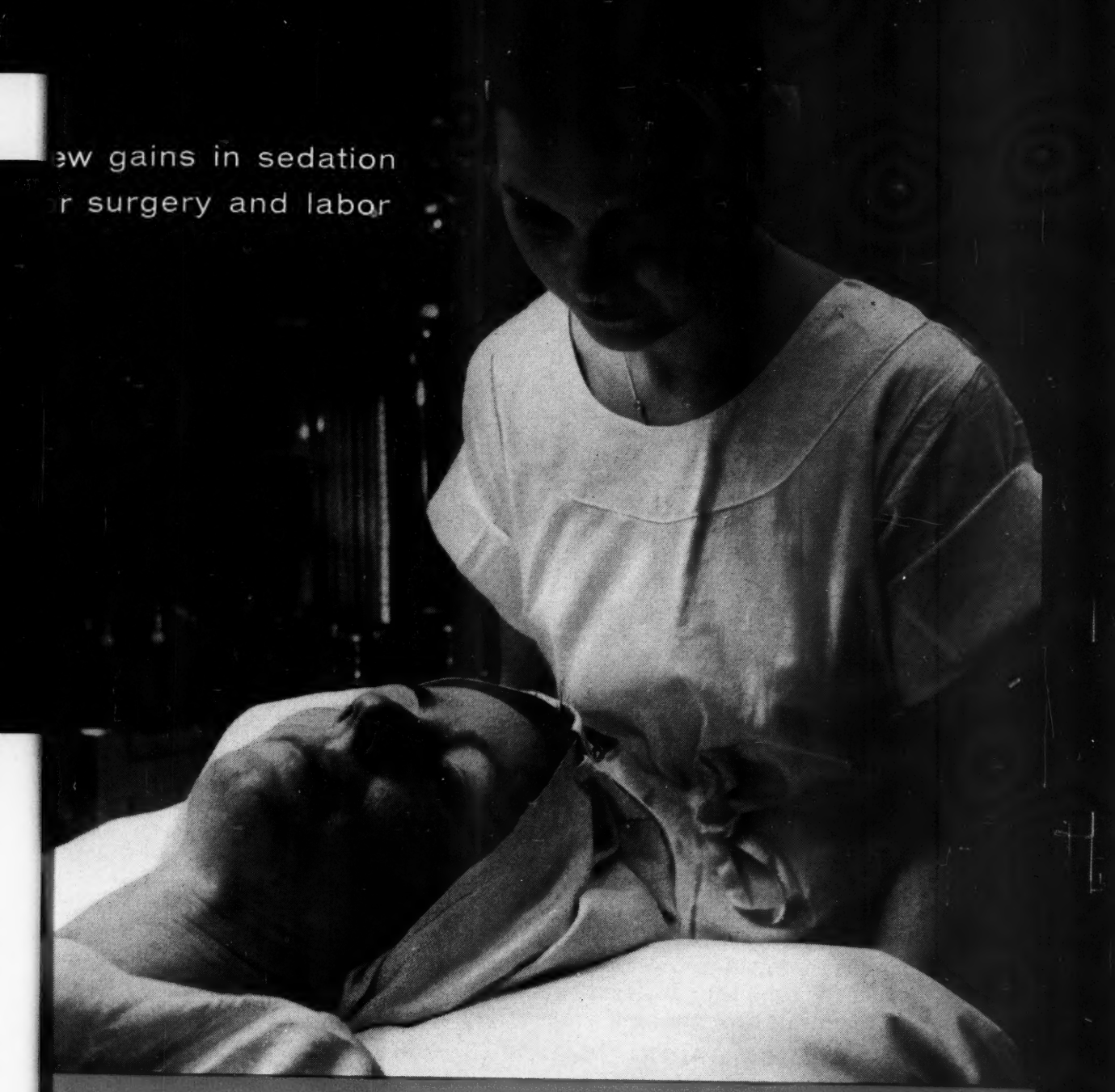
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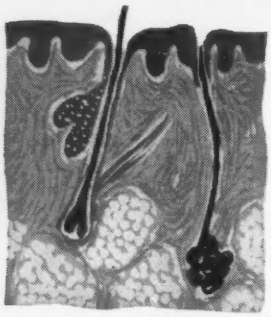
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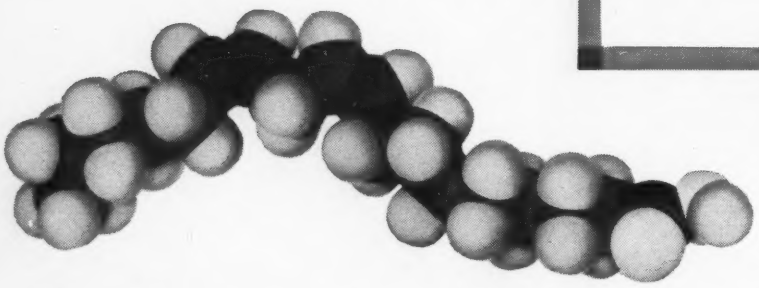
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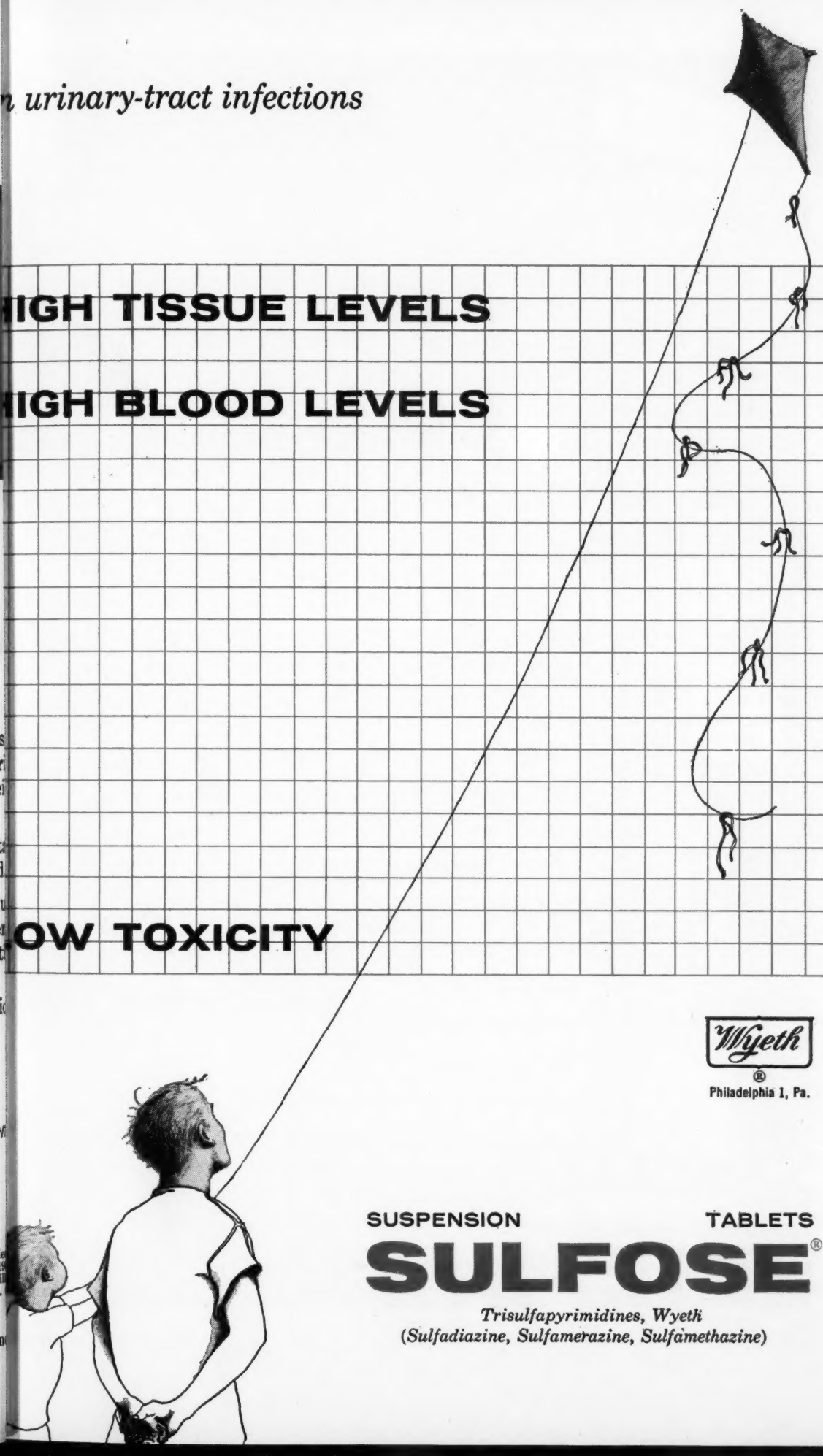
References:
1. Hansen, A. E.; Adam, D. J. D.; Boelsche, A. N.; Haggard, M. E.; Wie H. F.; Pratt, E. L., and Hunter, V.: Fed. Proc. *16*:387, Part I (March) 19
2. Macy, I. E.; Kelly, H. J., and Sloan, R. E.: The Composition of Mil Publication 254, Washington, National Research Council, rev. 1953, p.
3. Hansen, A. E., and Burr, G. O.: J. A. M. A. *132*:855 (Dec. 7) 1946.

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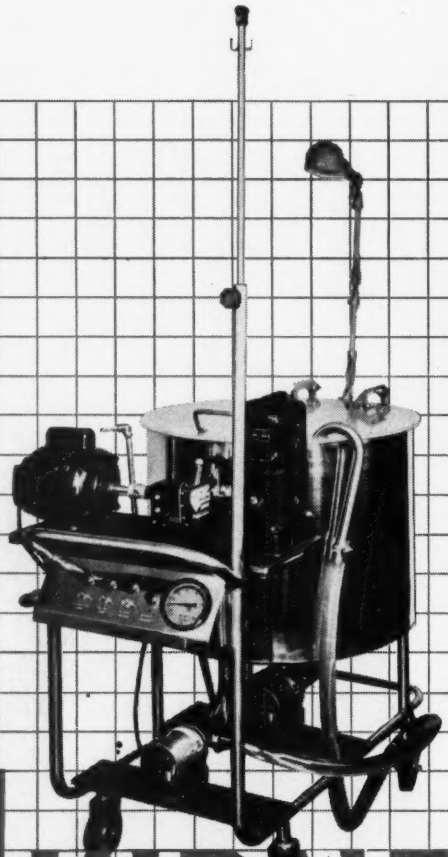
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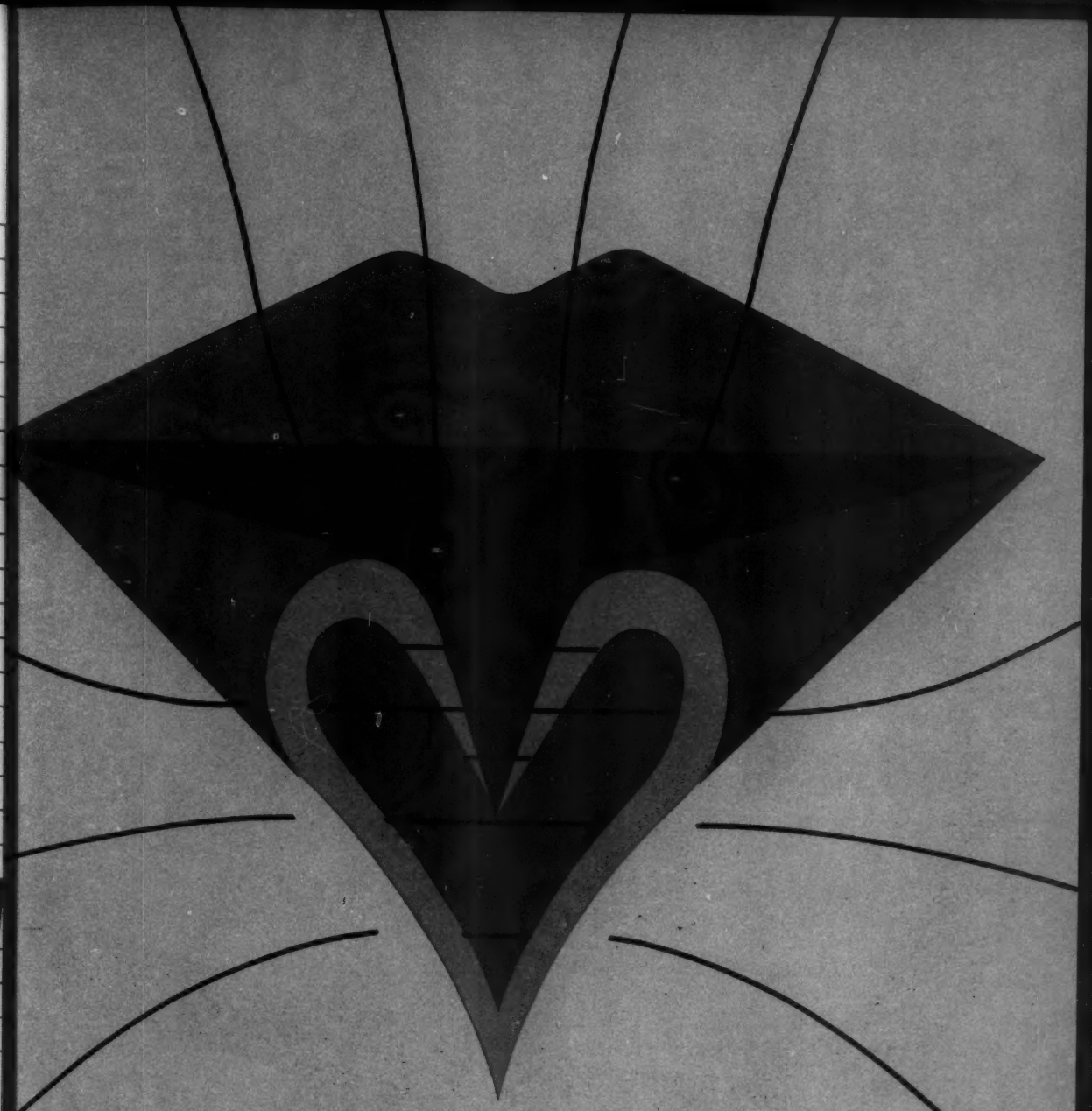
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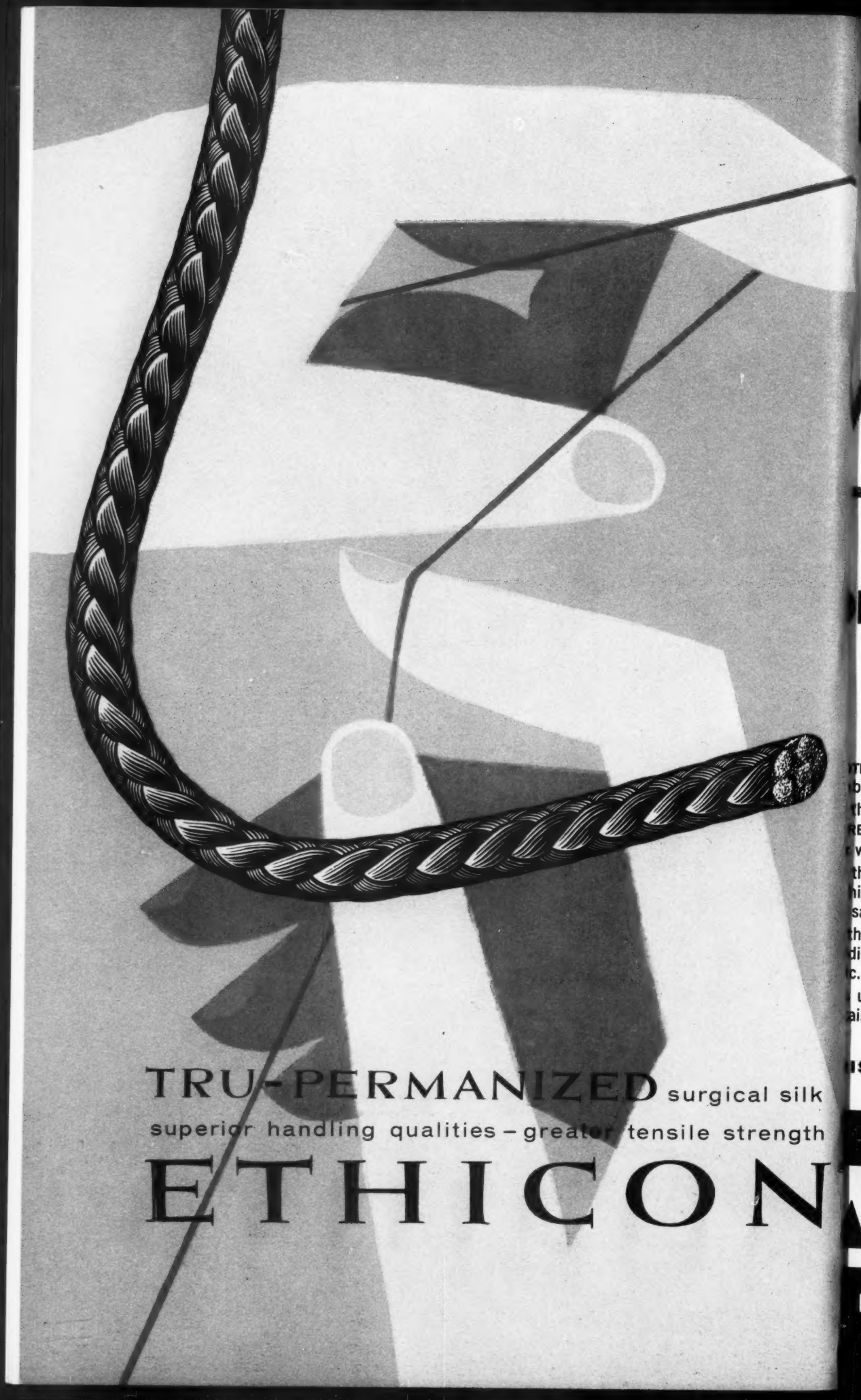
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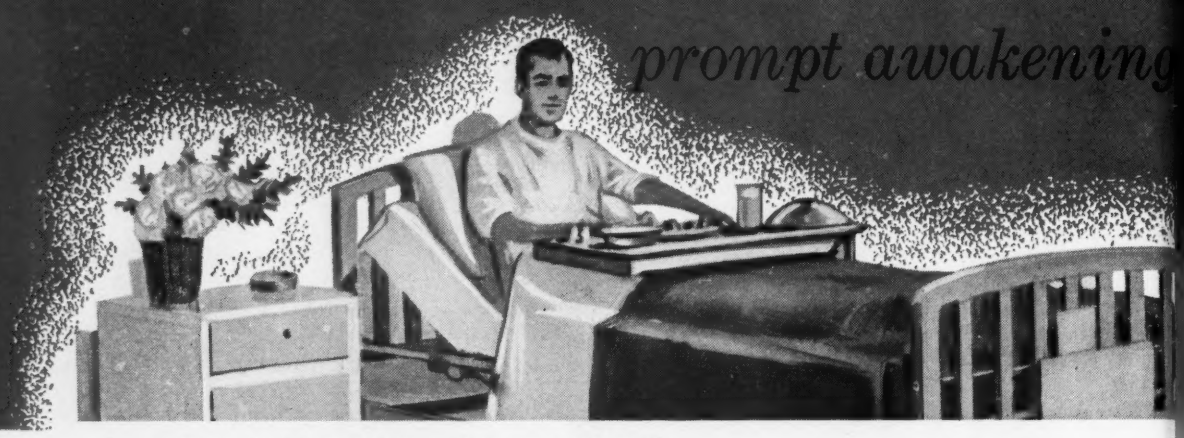
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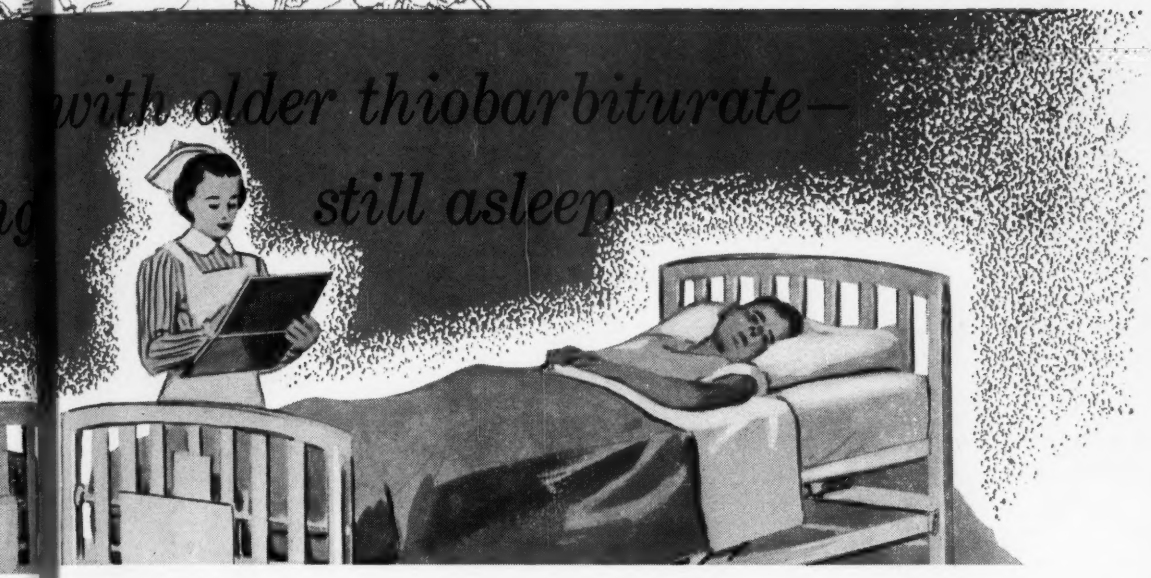
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(1) Boone, J. D.; Muñoz, R., and Dillon, J. B.: Anesthesiology *17*:284, 1956. (2) Zima, O.; von Werder, F., and Hotovy, R.: Anaesthesist *3*:244, 1954. (3) Mersch, M. A.; Clarie, D'A., and Fitzpatrick, L. J.: J.M. Soc. New Jersey *53*:414, 1956. (4) Blake, M. W., and Perlman, P. L.: J. Pharmacol. & Exper. Therap. *117*:287, 1956. (5) Irwin, S.; Stagg, R. D., Dunbar, E., and Govier, W. M.: J. Pharmacol. & Exper. Therap. *116*:317, 1956. (6) Ayd, F. J., Jr.: Neraval: A new anesthetic for electroconvulsive therapy, Paper presented at annual meet., Electroshock Research Association, Chicago, Illinois, April 29, 1956. (7) Reifferscheid, M., and Dietmann, K.: Deutsche med. Wchnschr *79*:638, 1954. (8) Houde, J., Hudon, F., and Jacques, A.: Neraval (methitural sodium), Paper presented at Meet., Canad. Anaesth. Soc., Quebec City, P. Q., May 5, 1956.

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A.
Introduction.
The Relation of the Electrocardiographic Deflections to Mechanical and Electrical Events in the Cardiac Cycle.

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* * *

C.
Origin and Form of the Normal and Abnormal QRS-T Complex.

* * *

D.
Disorders of Rate and Rhythm.

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E.
Summary of QRS-T Patterns in Unipolar Thoracic and Limb Leads.

This work is the outgrowth of previous manuals prepared to supplement the Graduate Course in Electrocardiography given at Wayne University College of Medicine for many years. The objective is an organized presentation of the interpretation of the unipolar electrocardiogram. The only basic physics included is that considered essential to the interpretation of the tracing; controversial theories that do not contribute to clinical analysis have been omitted.

The analysis of the arrhythmias is made from leads that clearly display auricular as well as ventricular deflections; the interpretation of the QRS-T complex is based upon the findings in multiple precordial and back leads, supplemented, when necessary, by esophageal and unipolar limb leads. The registration of the normal and abnormal QRS-T complex is based upon concepts developed by Frank N. Wilson and associates and shown to be consistent with experimental and post-mortem findings. These concepts have been presented in detail and suitably illustrated with diagrams as an introduction to clinical analysis. Efforts have been concentrated on a systematic lucid description of electrocardiographic findings in an attempt to make reproduction of tracings unnecessary.

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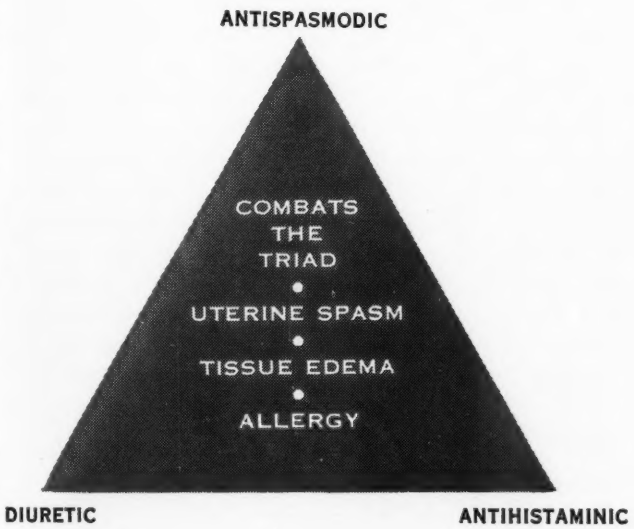
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In the preparation of this revision an attempt has been made to conform to the purpose of the original author—to develop a practical aid to physicians who are meeting and contending with obstetric difficulties and emergencies. Because the general practitioner is often the first to see the complicated cases, the revisor has made a special attempt to make the new edition of as much practical value as possible to the general practitioner without destroying its value for the specialist. To accomplish this he has included methods for the management of pregnancy and its complications which can be utilized in small general hospitals or at home, as well as in large well-staffed maternities.

A brief chapter on normal labor and another concerning the normal puerperium as a basis for the discussion of the management of complicated delivery and of postpartum disorders have been added. The changes which occur in the maternal organism in response to pregnancy are not consolidated in a separate section but are considered as they relate to and influence each of the complications. In some instances the material was rearranged to permit a single complete discussion of certain conditions rather than to describe their treatment during pregnancy, labor and the puerperium separately; the management of the third stage of labor and the treatment of postpartum hemorrhage, for instance, are considered together, and breech delivery is combined with version and breech extraction which are similar in many respects. The portions of the book on erythroblastosis fetalis and the examination and care of the newborn infant were prepared by Dr. Victor C. Vaughan, III, Assistant Professor of Pediatrics in the Temple University School of Medicine.

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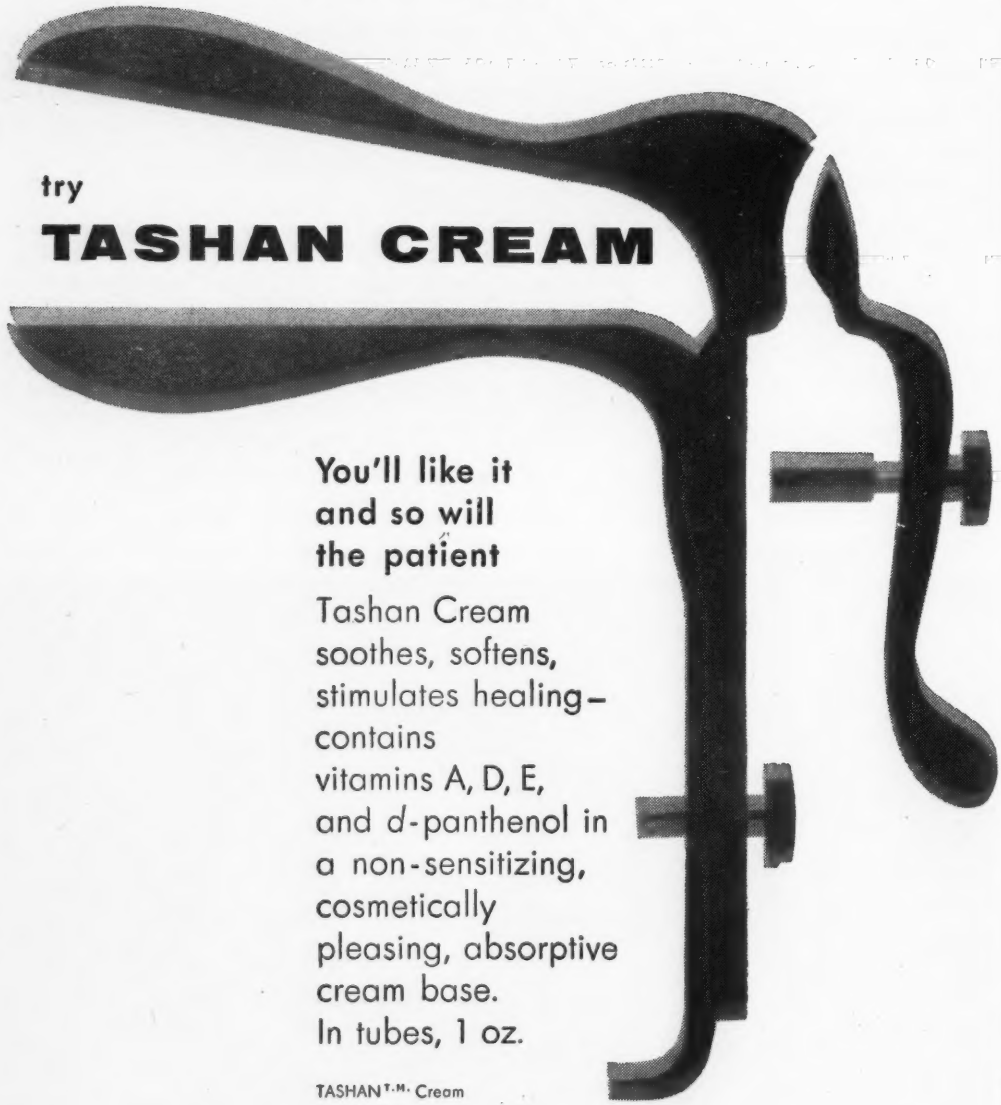
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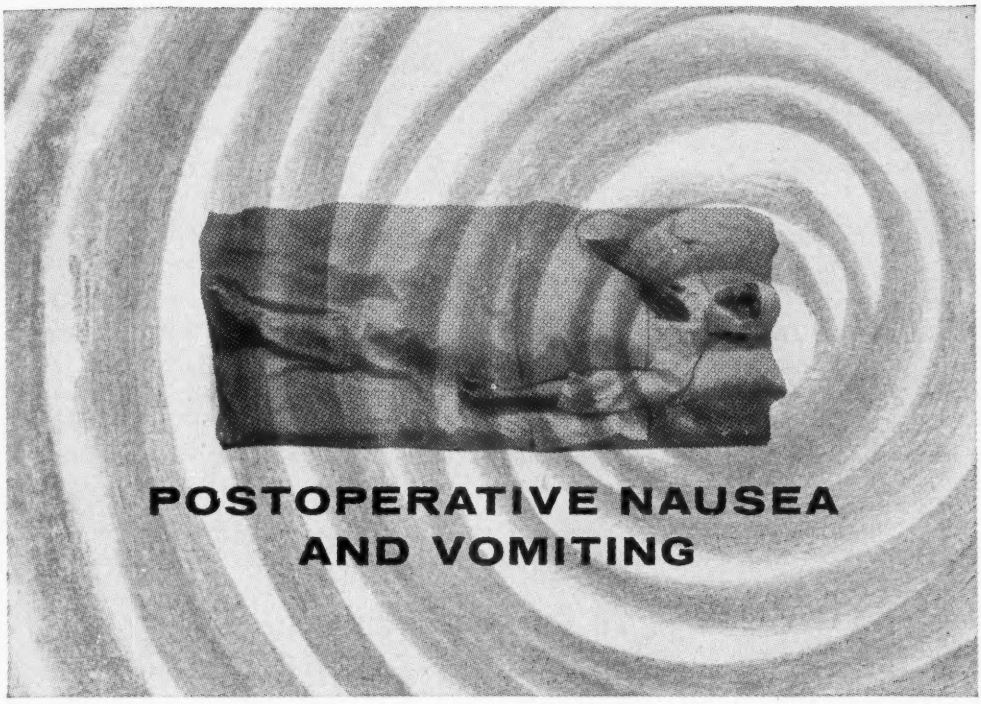
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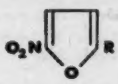
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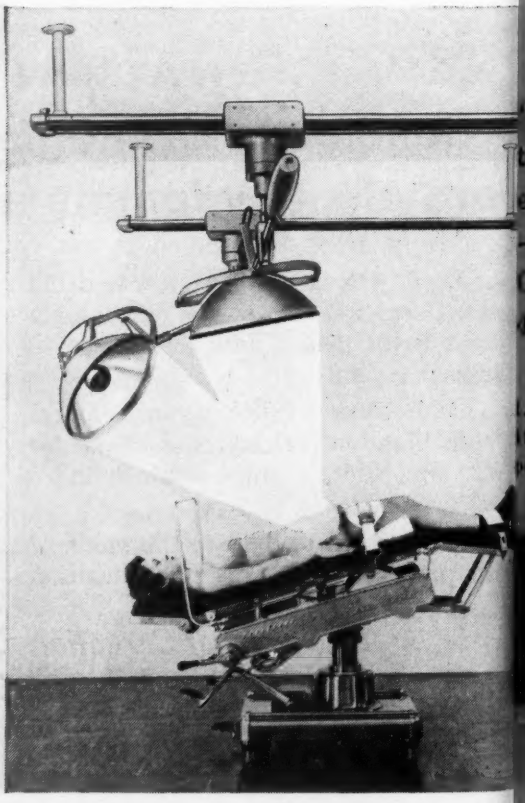


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1. Doyle, J. C.: California Med. *71*:15 (July) 1949. • 2. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 3. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657.

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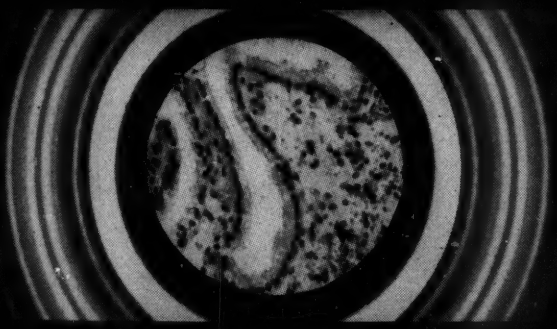
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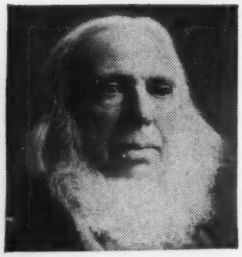
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in postmenopausal vaginitis

in vaginal plastic surgery

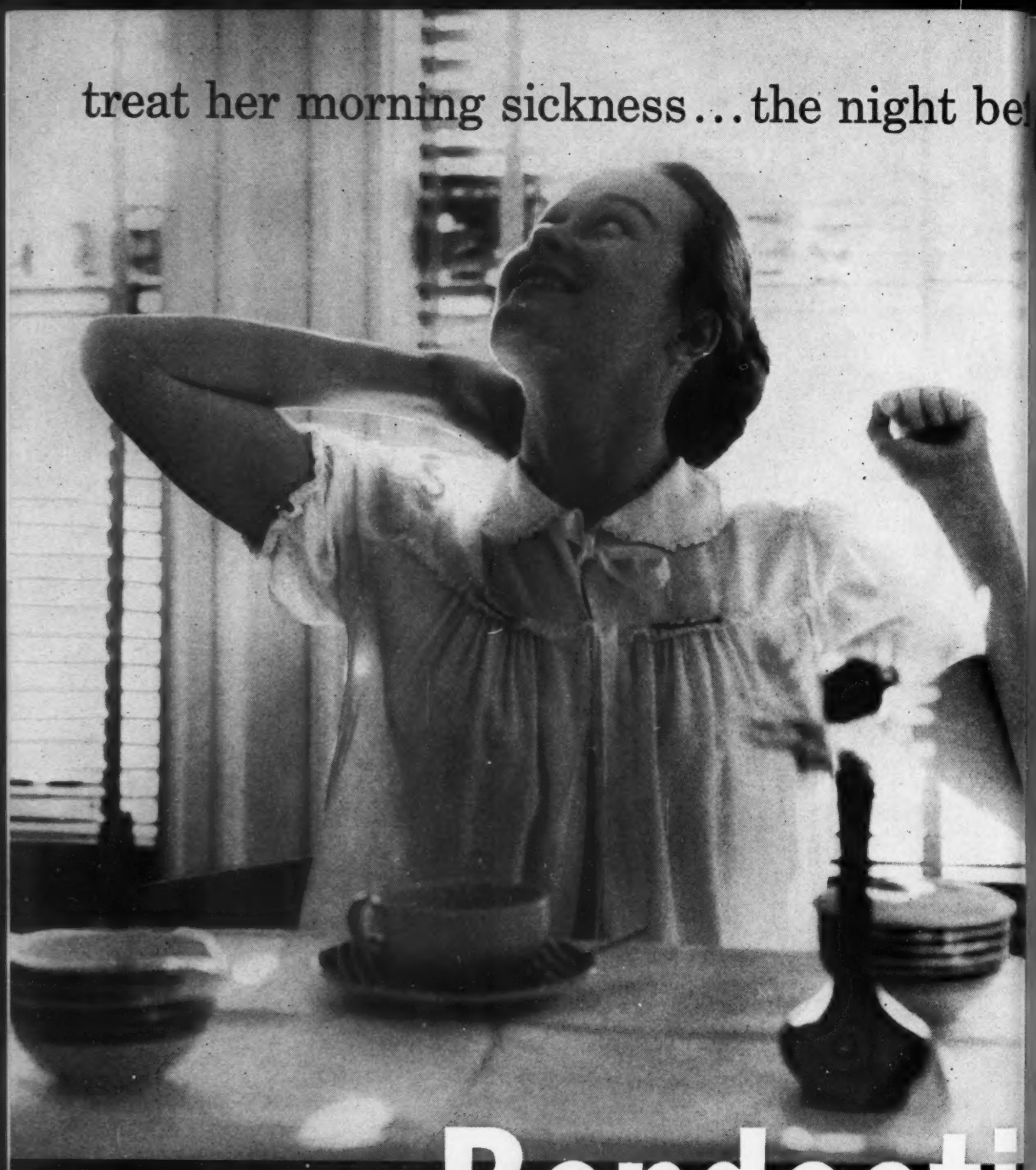
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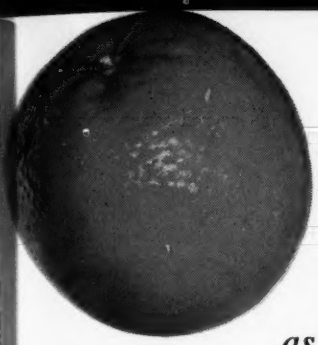
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1. Nuisen, R. O.: Ohio State M. J. 53:665, 1957.
2. Clinical communications, 1956-57.

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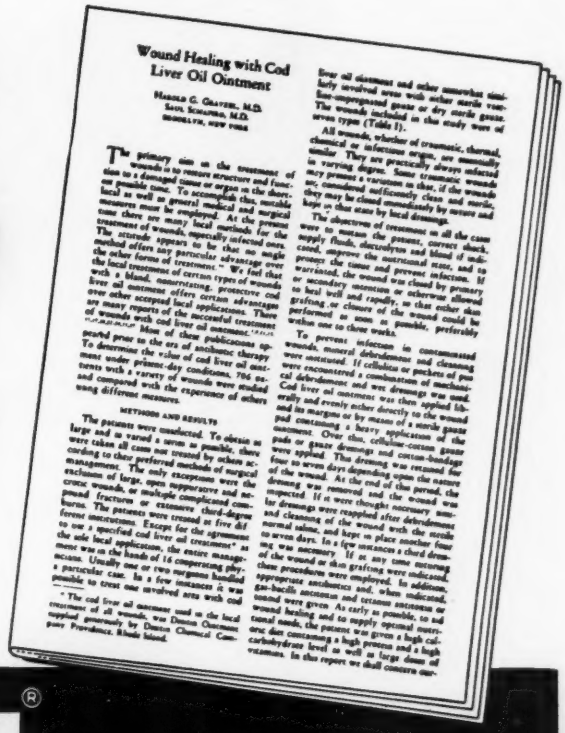
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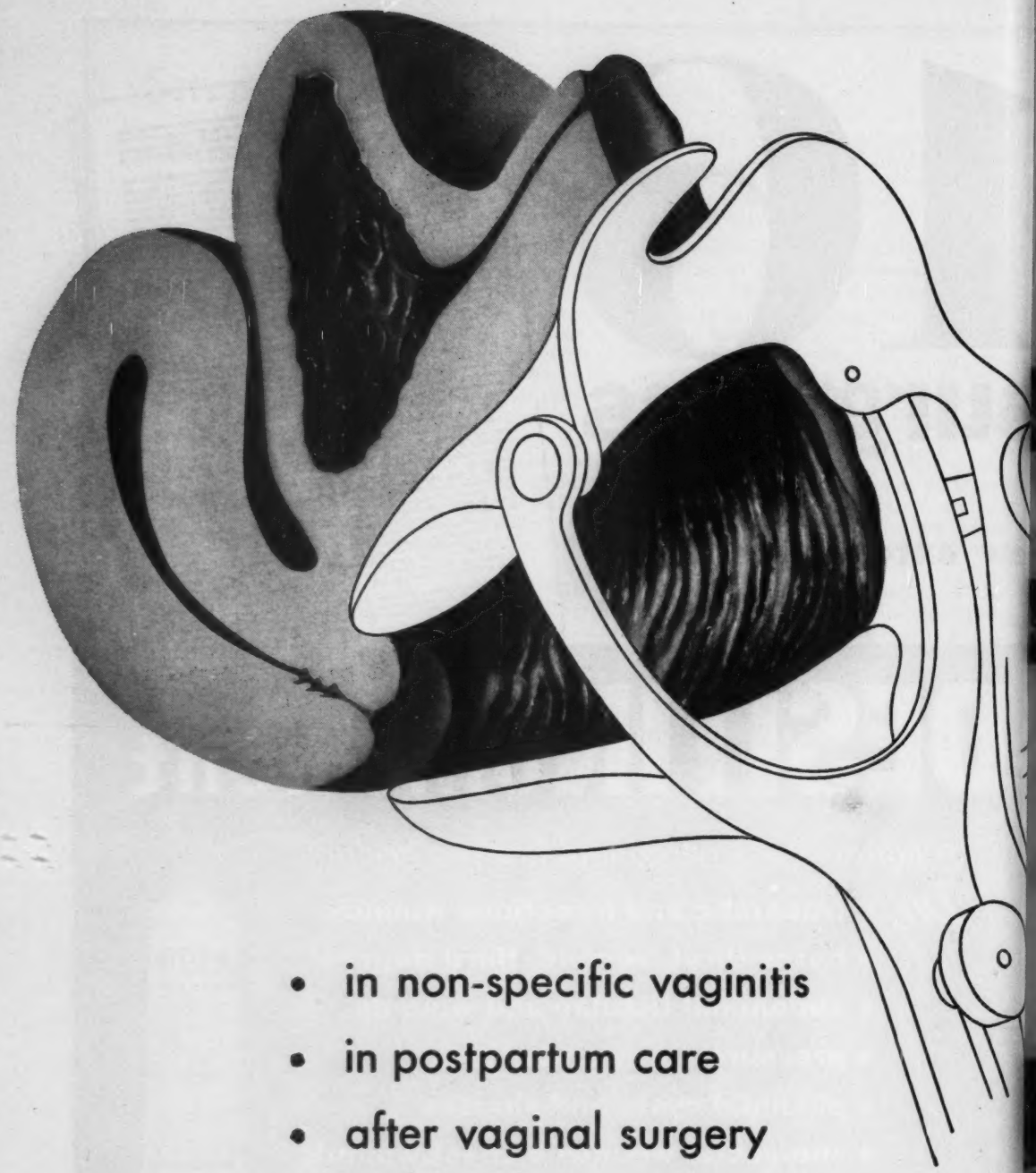


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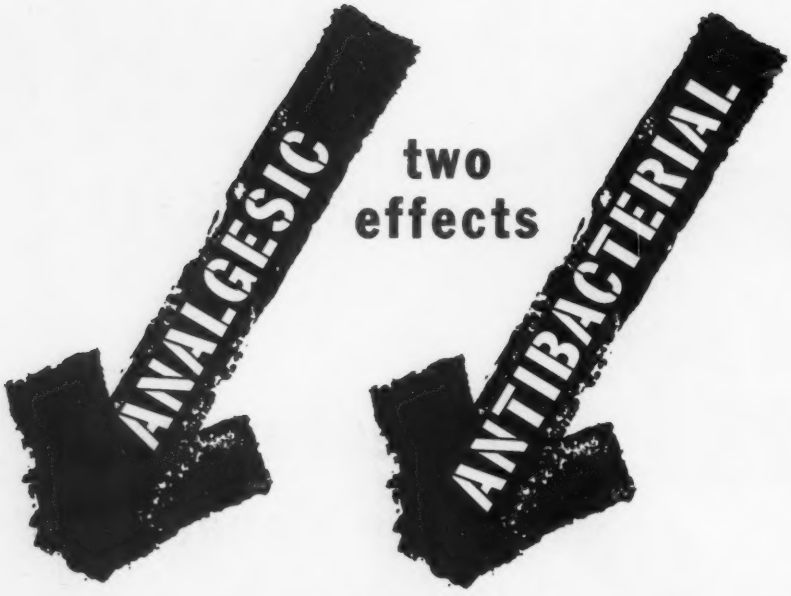
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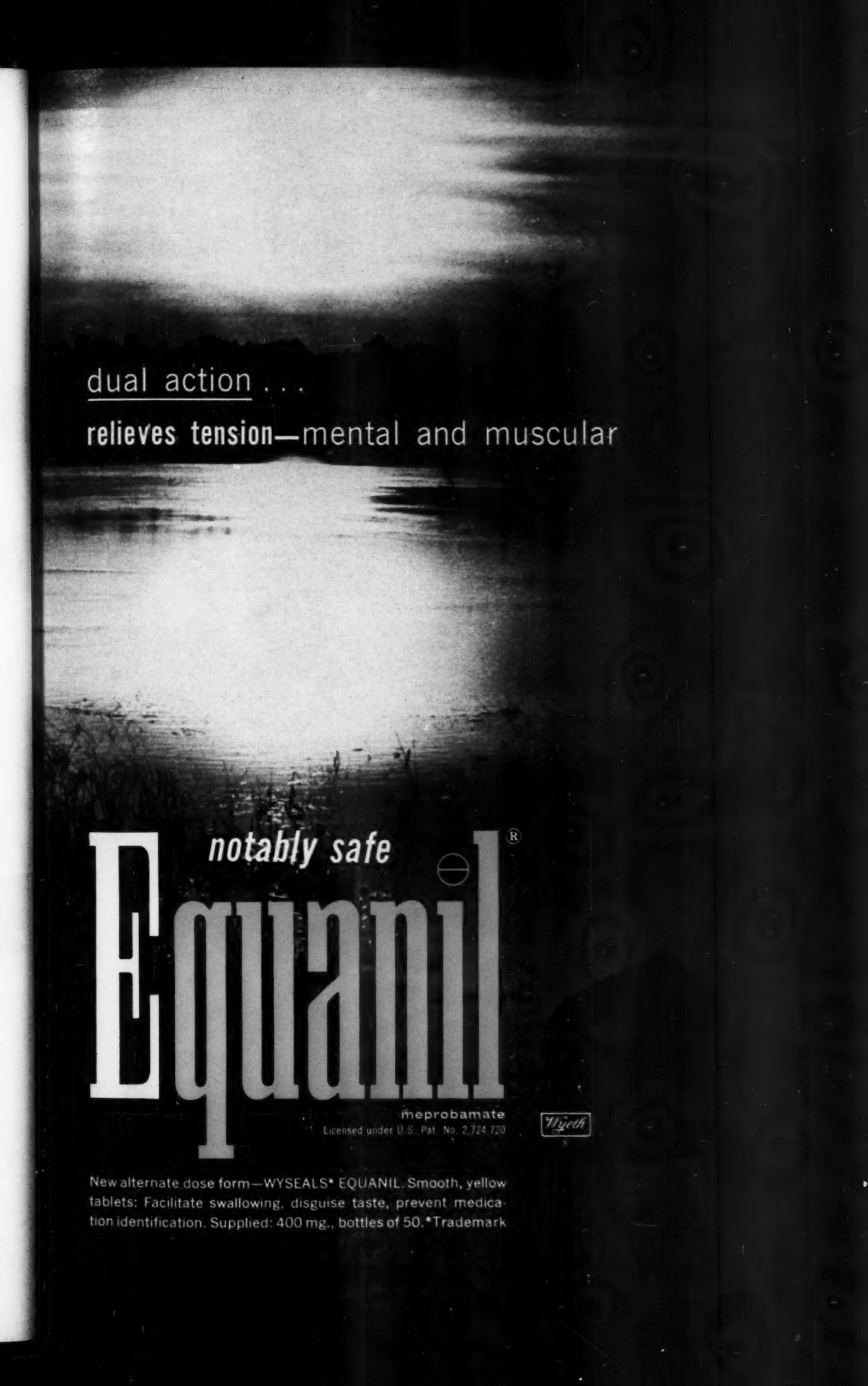
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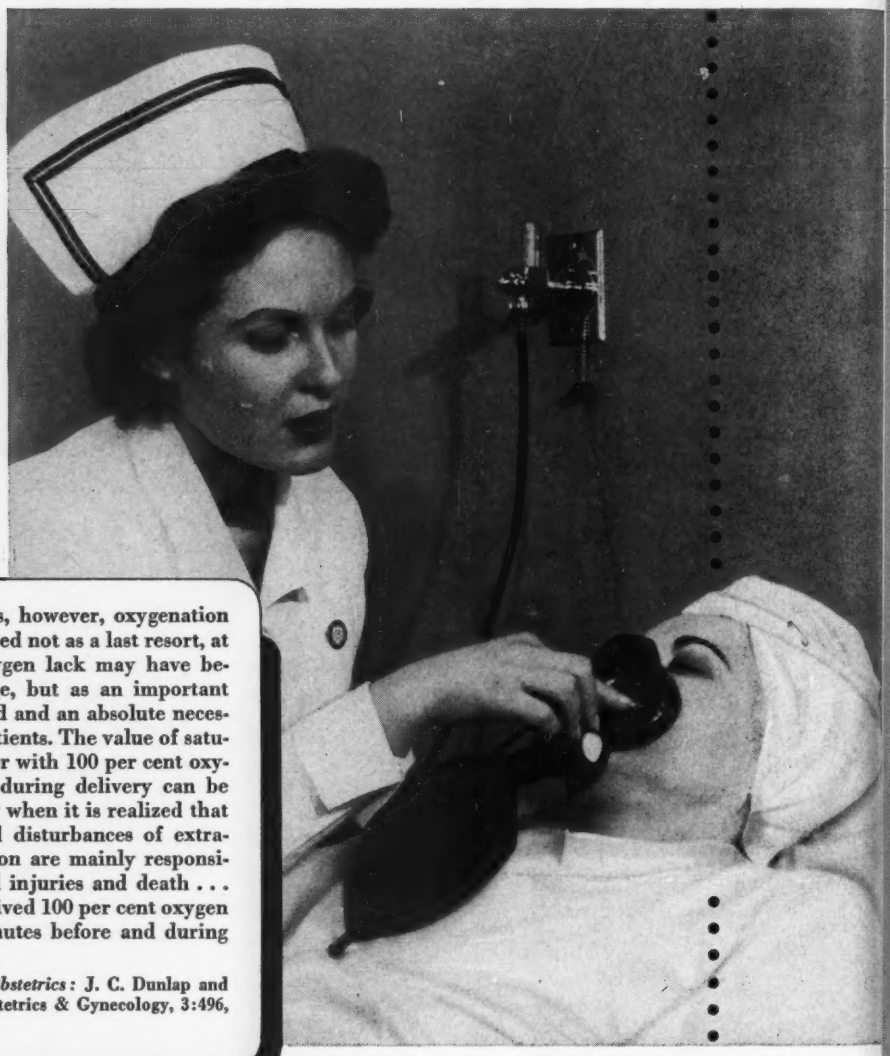
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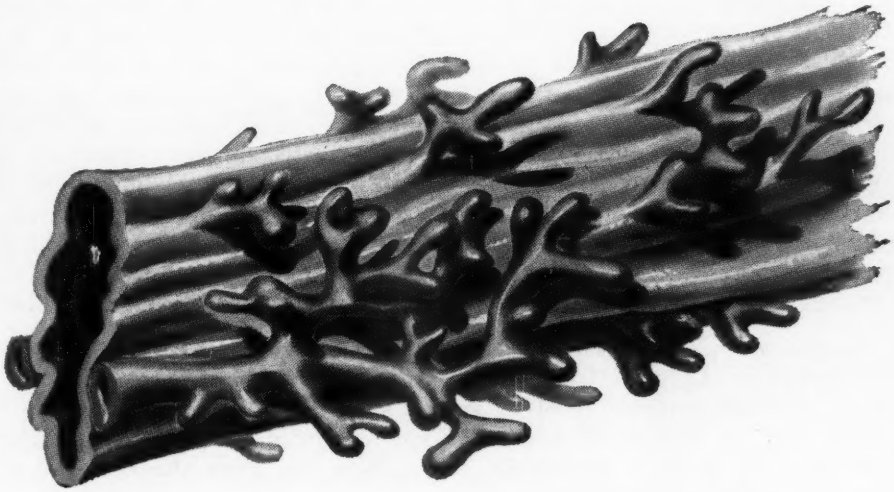
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rediscovered:

the female urethra

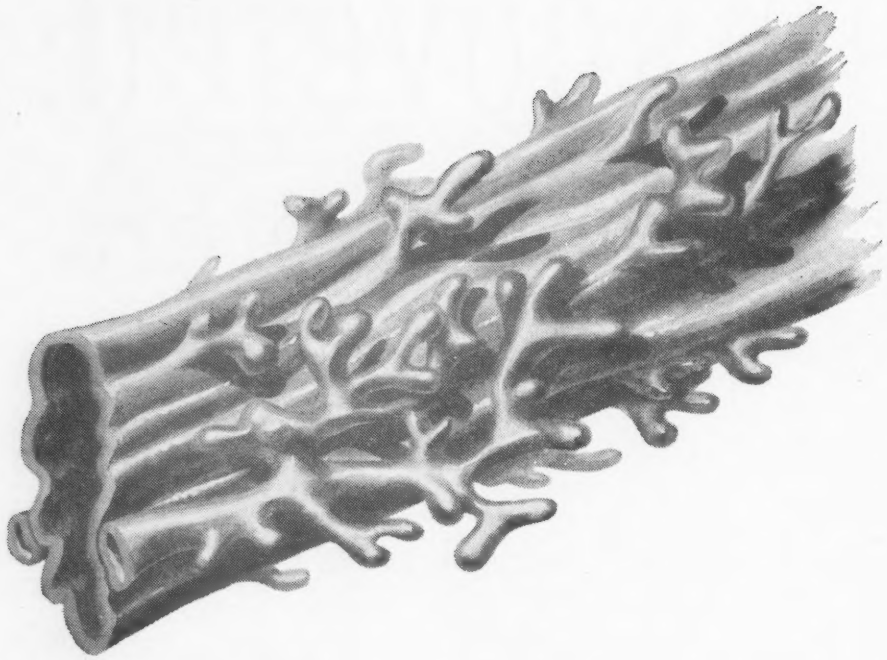
newer knowledge of its structure and cytology provides a clearer understanding of its important role in pelvic distress.



Schematic construction of female urethra demonstrating extensive network of peri-urethral glands, ending in numerous blind pockets. Drainage is into the urethra through small openings along its length, and into the para-urethral (Skene's) ducts.

1. Recent anatomic studies of the female urethra demonstrate a high susceptibility to infection.

A changing concept—The female urethra "was formerly considered only to be a short, simple, straight tube which served solely to empty the bladder. Recent studies have changed our notions concerning this . . . . sections through the urethra and its surrounding tissues have shown numerous glands."[1]



Tortuous, with many interconnections but relatively poor drainage, these glands "form ideal foci for chronic infection."[1] Periurethral gland infection is followed by infiltration and thickening of the urethral wall, hypertrophy and granulation of the urethral mucosa, and constriction of the urethral lumen. The trauma of childbirth and coitus further invites infection of these delicate structures, which are exposed to vaginal and rectal discharges "from the period of diaper life to old age."[1] Thus, the urethra is not only a portal of entry for urologic infection, but the *site* of pathologic change "more frequently than any other portion of the female urinary tract."[2]

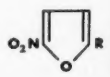
Unrecognized source of pelvic symptoms—Prevalent as it is in women, chronic urethritis "can be easily overlooked" because of the frequency with which the pain and discomfort are referred to other areas.[2] In addition to obvious urinary tract symptoms such as frequency, urgency, pain and burning on urination, chronic urethral infection is often responsible for pain in the lower abdomen and pelvis, lumbosacral region or upper thighs.

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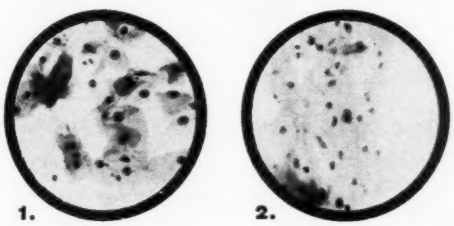
The Nitrofurans—a unique class of antimicrobials . . . Products of Eaton Research

2. Exfoliative cytology explains frequency of dyspareunia and other pelvic complaints in postmenopausal women.

Senile urethritis: often encountered, seldom described—A little known phenomenon has recently been reported by Youngblood and his colleagues.[4,5] Examining smears of epithelial cells from the urethrae of postmenopausal women, they found the same absence of normal, cornified, pyknotic squamous cells as in the vaginal smears, resulting from estrogen deficiency. Leukocytes and even erythrocytes were usually present, as in senile vaginitis. Along with these cytologic alterations, endoscopic examination revealed a hyperemic and atrophic urethral mucosa.

"Senile" urethritis is a common cause of dyspareunia, dysuria and other pelvic discomfort in postmenopausal women. Even when the urethra is recognized as the trouble spot, these women frequently fail to obtain relief because the underlying involutional nature of the urethritis is unsuspected, and antibacterial measures alone are employed. The lesion may resemble closely that of nonspecific urethritis.

"Progressive histologic normalization" parallels rapid symptomatic relief with new Furestrol Suppositories. In their investigations, Youngblood and co-workers[4,5] treated 120 postmenopausal, involutional urethritis patients with FURACIN Urethral Suppositories containing, in addition, 0.1 mg. of diethylstilbestrol. All showed prompt alleviation of symptoms, with disappearance of endoscopic signs of irritation. After 1 to 2 weeks' treatment, the urethral smears returned to normal, indicating replacement of the atrophic mucosa with a healthy, stratified squamous epithelium. These FURACIN-estrogen suppositories are now available as FURESTROL Suppositories.



1. 2.

1. Pretreatment urethral smear of postmenopausal woman with senile urethritis. Basal cells with low nucleocytoplasmic ratio are predominant, with leukocytes and erythrocytes.

2. Urethral smear from same patient after 2 weeks' treatment with FURESTROL Suppositories. The cornified, squamous cells indicate a healthy, normal epithelium.

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REFERENCES: 1. Wharton, L. R. in Campbell, M.: Urology, W. B. Saunders Company, Philadelphia and London, 1954, Vol. 2, p. 1390 et seq. 2. Barrett, M. E.: J. M. Ass. Alabama 26:144, 1956. 3. Youngblood, V. H.: J. Urol. 70:926, 1953. 4. Youngblood, V. H.; Tomlin, E. M., and Davis, J. B.: Senile urethritis in women, J. Urol. (in press). 5. Youngblood, V. H.; Tomlin, E. M.; Williams, J. O., and Kimmelstiel, P.: Exfoliative cytology of the senile female urethra, Tr. Southeast. Sect. Am. Urol. Ass. (in press).

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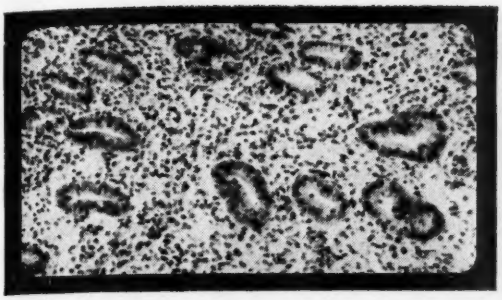
Regulates menstrual disorders through reliable endometropic control

Enovid is Searle's new, orally effective agent designed to provide specific control of menstrual disorders.

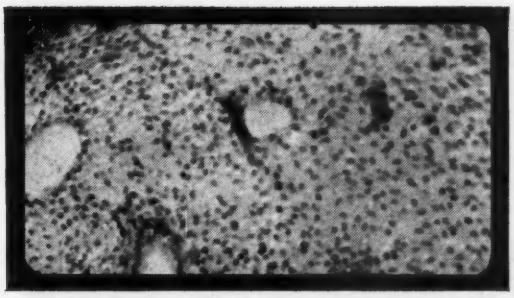
Enovid contains norethynodrel, a new synthetic steroid with strong progestational and lesser estrogenic activity. The estrogenic effect, enhanced by the addition of ethynylestradiol 3-methyl ether, prevents spotting or breakthrough bleeding in most patients in whom it would otherwise occur.

Like the normal endocrine action of the corpus luteum, Enovid maintains the integrity of the endometrium during administration of the drug. Moreover, as occurs on withdrawal of the natural hormone, the withdrawal of Enovid results in the flow characteristic of menstruation. Also, as does the natural hormone, Enovid controls the gonadotropic functions of the anterior pituitary glands.

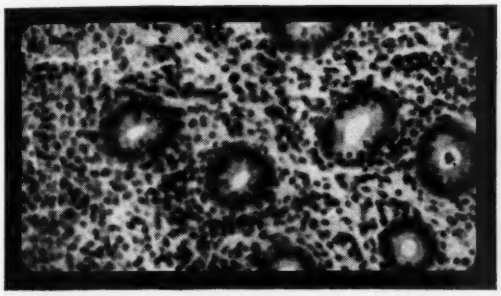
This specific control of the menstrual cycle permits effective treatment of both excessive and inadequate endometrial activity and provides a dependable agent for treating such disorders as amenorrhea, dysmenorrhea, menorrhagia, metrorrhagia and premenstrual tension.



Pretreatment biopsy of endometrium in anovulatory menometrorrhagia.
Interpretation: Proliferative endometrium.



Post-treatment biopsy on day 25 after 10 mg. of Enovid daily from day 5 to day 20.
Interpretation: Late secretory endometrium with pseudodecidual stromal development.



Post-treatment biopsy (second treated cycle) on day 19 after 5 mg. of Enovid daily from day 5 to day 19.
Interpretation: Early secretory endometrium with slight pseudodecidual reaction.



Pretreatment biopsy from patient with anovulatory menometrorrhagia.
Interpretation: Proliferative endometrium.

INDICATIONS AND DOSAGE GUIDE FOR ENOVID

DISORDER	FIRST CYCLE	SECOND AND THIRD CONSECUTIVE CYCLES
Menorrhagia	One or two 10-mg. tablets daily to day 25 of the cycle	One 10-mg. tablet daily from day 5 to day 25*
Metrorrhagia	One or two 10-mg. tablets daily to day 25 (or for 10 days to establish cycle)	same as above
Amenorrhea (primary or secondary)	One 10-mg. tablet daily for 20 days to establish cycle	same as above
Oligomenorrhea	One 10-mg. tablet daily from day 5 to day 25*	same as above
Premenstrual Tension	One 10-mg. tablet daily from day 5 to day 25*	same as above
Dysmenorrhea	One 10-mg. tablet daily from day 5 to day 25	One 10-mg. tablet daily from day 5 to day 25
Inadequate Luteal Phase	One 10-mg. tablet daily from day 15 to day 25	One 10-mg. tablet daily from day 15 to day 25

*The administration of Enovid prior to day 15 may interfere with ovulation; if anovulatory cycles are not desired, one 10-mg. tablet of Enovid should be administered daily from day 15 to day 25.

SPECIAL NOTES: (1) If nausea is encountered, the daily dose may be cut in half or given in divided doses for three days and then return to regular dose.

(2) Intermenstrual spotting is usually evidence of inadequate dosage. This type of bleeding is usually controlled by increasing the dosage one 10-mg. tablet daily. (3) Following discontinuance of treatment, the intermenstrual interval of the first untreated cycle is commonly prolonged for approximately one week.

FORMULA: Each 10-mg. tablet of Enovid (available as uncoated, scored, coral tablets) contains norethynodrel, a new synthetic steroid, with 0.15 mg. of ethynylestradiol 3-methyl ether.

Biopsy photomicrographs courtesy of Anna L. Southam, M.D., New York, N. Y.

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ASCORBIC ACID	600 mg.	Riboflavin	4.5 m
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Calcium Pantothenate	6 mg.	Vitamin B_{12}	4.5 m
Calcium Carbonate (500 mg. calcium)	1.25 Gm.	Folic Acid	0.3 m
Vitamin A Acetate	6,000 U.S.P. Units	Pyridoxine Hydrochloride	10.0 m
Vitamin D_2	1,200 U.S.P. Units	Copper Sulfate (3.0 mg. copper)	12.0 m
		Potassium Iodide (0.3 mg. iodine)	0.4 m

Providing the daily requirements or more of vitamins and iron during pregnancy as recommend by the National Research Council.

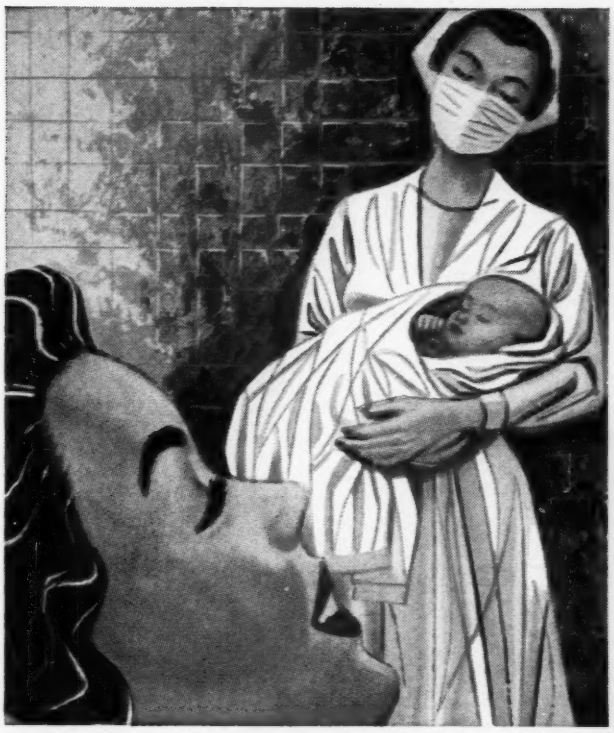
1. Greenblatt, R. B.: Obst. & Gynec. *2*:530, 1953.
2. Dill, L. V.: M. Ann. District of Columbia *23*:667, 1954.

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REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
3. Karnaky, K. J.: South. M. J. 45:1166, 1952.
4. Peña, E. F.: Med. Times 82:921, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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Vol. 74, No. 4
October, 1957

American Journal of
OBSTETRICS AND GYNECOLOGY

American Gynecological Society
Transactions of the Eightieth Annual Meeting

GYNECOLOGY—WHITHER BOUND?*

Presidential Address

NORMAN F. MILLER, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan)

IN CHOOSING to address you from a gynecological point of view I am not unmindful of obstetrics. It is simply that I believe gynecology is in greater need of appraisal. Some of my remarks will apply with equal validity to obstetrics.

The future of gynecology fascinates me, but any attempt to foresee its destiny implies a prophetic ability which I do not possess. I claim acquaintance, however, with the recent past as well as the present, and have scanned both to determine whether we may derive therefrom some guidance for the future. Such appraisal reveals abundant evidence of improvement. Indeed, the last half century has probably witnessed greater progress than the entire previous history of gynecology. This has occurred in an era marked by tremendous progress in all branches of medicine and we have abundantly profited thereby. On this, the favorable side of the ledger, there is little need for elaboration. Generally speaking, we have accepted basic discoveries from all branches of science and adapted them to the needs of our patients. The fact that gynecology, like other branches of medicine, has had an exhilarating ride on the

*Presented at the Eightieth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 27-29, 1957.

coattails of discoveries chiefly in other fields of science may, however, have created a false sense of achievement. Such progress must not blind us to some less acceptable aspects of gynecology. Let us, therefore, take a second look.

I recognize four areas requiring attention, namely: (1) a shrinking imagination, (2) a seemingly endless reportorial circling, (3) a lack of adroitness in professional conversation, and (4) a pedagogical one-sidedness. While these shortcomings are doubtless present in other fields of medical endeavor their correction in gynecology is our job. Let others follow if they will.

Lack of imagination in gynecology is seen chiefly in the technical areas so let us look first in this direction. Although training, personal preference, and opportunity may lead us in different paths, the advancement of gynecology is a task to be shared by us all. Just how we can contribute will, of course, vary with our individual abilities and opportunities. Whether it be meditation on a gynecological problem with the aim of clarifying our own understanding, the encouragement of research by others, or active participation in clinical or laboratory investigation is at the moment of less importance than recognition of the need to participate. Participation in any of these areas is not something one suddenly embarks upon in the spirit of the moment. For some people scientific reconnoitering is natural and satisfying. For others the taste is acquired. First comes the motivating curiosity, the sign of a probing mind. Then, tuned to the endeavor, comes the struggle for accomplishment. If, as I believe, we have been weak in imagination and lax in offering leadership and encouragement, it appears we may have been equally culpable in our failure to provide space and facilities. Concern over these things has been voiced by Fellows of this Society on more than one occasion. Fortunately, competent appraisial of research facilities in gynecology is now well under way—thanks to the effort of some of our Fellows.

While uneasiness over the dearth of gynecological research is probably justified, I am more concerned about the lack of imagination in the practice of gynecology, especially gynecological surgery. Once a dominant field of endeavor, surgery of the female reproductive tract has notably lessened. To a degree this reflects progress in the form of reduced birth trauma and control of infection. It may reflect a better understanding of functional disorders and imply greater knowledge regarding the control of symptoms without organ extirpation. If the lessening of gynecological surgery were entirely the result of increased knowledge and the substitution of more suitable medical therapy, we could accept with equanimity such evolutionary change. Unfortunately, this is not the sole explanation, for it appears that we have also decreased our efforts. Our surgical repertoire appears to have shrunk to operations for either the removal or the support of the uterus and adjacent structures. Only now and then are there imaginative attempts to go beyond the conventional. With few exceptions gynecological surgery finds itself in the doldrums. Take perineorrhaphy, a procedure nearly every physician considers himself competent to perform. One commonly accepted technique includes lassoing the levator ani muscles in order to bring about their approximation in the midline. This

procedure is neither anatomically nor physiologically ideal. The tautness with which these structures are pulled together commonly makes the operation surgically unsound. Presumably, restoration of the perineal body is undertaken for purposes of support and restoration of function. While the support thus provided is often good, the functional result frequently constitutes the last chapter in a woman's sexual life. Perhaps this is to be expected, since textbooks on gynecology have little to say regarding the surgical anatomy of the perineal body and even less about the dysfunctional consequences of a rigid, high perineum. There is need for a better understanding of the anatomy of the perineal body. Similarily, the surgical techniques for its repair are in need of revision. The so-called fascial repair is a step in this direction. That we are commonly unimaginative in our surgical thinking is also illustrated in the treatment of uterine fibroids. We accept these familiar tumors with seldom a thought as to why they occur. Furthermore, we frequently credit them with unwarranted symptoms. Although they may be present in a bleeding uterus, the fibroids themselves rarely bleed. When treatment is undertaken, our lack of imagination seldom leads to anything but hysterectomy (and perhaps oophorectomy). Ostensibly the tumor is the object of concern, yet myomectomy is seldom carried out. When necessary, let us dispose of the uterus with its tumors, but let us recognize that we are shooting at the target with a blunderbus instead of a rifle.

We stress the desirability of preserving reproductive function, yet in the management of tubal pregnancy we invariably sacrifice the tube. Tubal abnormality or disease may have predisposed to the ectopic implantation, consequently preservation of the involved tube may be undesirable. But, how can we know that this is so until we have adequately tried it?

The need for a review and revitalization of gynecological surgery is by no means confined to the areas mentioned. Solutions of such problems as anomalies of the reproductive tract, occluded Fallopian tubes, stress urinary incontinence, reconstruction of genital organs, as well as new approaches to the correction of extensive relaxation, especially prolapse, are all awaiting full-scale appraisal and possible revision.

Here are needs and opportunities for constructive thinking. Here, too, are some words of caution. In contemplating change in surgical technique let us not mistake trivia for basic improvements, and let us not substitute uninhibited tinkering for sound surgery. "We must saddle our dreams before we ride them."

The spread of medical knowledge by means of the written word is a valuable weapon in the fight against disease. It can bring new information and techniques to physicians everywhere; it also records for the future our assets and liabilities. Writing has an important place in medicine, but we can have too much of it. In medicine, we sometimes mistake verbosity for proficiency. Reportorial activity does not establish medical competence. Yet this deep-seated belief is creating a frustrating problem. We must keep up with an ever-fattening medical literature without commensurate compensation in the form of new or useful information. Much of what appears in our gynecological

journals is rewarding. Yet perusal of titles over a period of years shows repetition to be commonplace. Though a report may contain nothing basically new, it may present a useful variation on something old. Many articles represent fresh versions of twice-told tales, but the authors' familiarity with a previous version is not always apparent. Since bulging journals are presumed to reflect industry there can be no denying the presence of spirit and ardor within our ranks. Among the published reports are those based on original research. Some of these are so written that they confuse the reader, and sometimes, I suspect, the author as well. Indeed, one is occasionally impressed by the fact that so much can be written about so little. But, reportorial excess is only one side of the problem. There is another, more shadowy, side. Published reports commonly laud this or that, but seldom is there a disapproving critique. Our literature is replete with recommendations on therapy and techniques, yet despite their prompt discontinuance by the author we are seldom enlightened by a correction or retraction. Thus the unwary may be misled by following a therapeutic program once advocated but long since discarded. No one denies the potential value of a progress report, but when the study is complete—when the therapy or technique has been tested and proved deficient—we then wish to know the truth, even though it means retraction of previously expressed opinion. Perhaps the creation of a review journal devoted to the revision or retraction of previously expressed opinions would be helpful. Such a publication might reduce the number of half-baked, inadequately proved recommendations which now find their way into our periodicals.

Medical writing and publishing pose problems and their solution is not simple. I doubt that curtailment of writing is either possible or a proper answer. A restriction on the length of articles and the development of abstract journals are matters deserving consideration. These tasks deserve more than editorial board attention. Everything in life changes except the number of hours in a day. Finding time for increased reading and—what is equally important—for moments of meditation, the lack of which we already abundantly demonstrate, is becoming more and more difficult. If we must write or encourage medical writing, let us place a premium on brevity. As literature may reflect the stature of an age, so perhaps our present literary redundance reflects the current zeal for writing in our speciality.

Although I mentioned professional discourse and pedagogical one-sidedness as two separate items, they are so closely related as I use them that I shall consider them together.

Art is still essential in the practice of medicine. Yet this important component has taken a severe pushing about by the tremendous growth of science; so much so as frequently to render the patient-physician relationship both disappointing and disturbing. Telling a patient about the presence of disease may be easy or difficult, but it is always important. Most physicians endeavor to do this with skill and tact, yet too frequently its accomplishment falls short and the patient is left bewildered and apprehensive. Furthermore, today patients may seek consultation without disease but leave with the first seeds of concern firmly implanted in their minds. A truthful exposition of findings

is desirable and the manner of their presentation is of considerable consequence. Unfortunately, the attainment of a medical degree has seldom been accompanied by more than perfunctory ability in expression and tact. Ineptness and bungling in the exposition of even unimportant findings all too often arouse apprehension in the receptive mind. The chain of events may begin innocently enough with a simple, truthful statement regarding a minor ailment. When inadequately explained, and therefore misunderstood by the patient, this may prey upon her mind until she becomes emotionally ill. Small wonder she consults other physicians. Perhaps they recognize her dilemma and succeed in reassuring her. Obviosuly, the original physician did not forsee this course of events. He is honest and conscientious, but he failed to recognize that what to him seemed so simple and unimportant was to the patient neither minor nor comprehended. The fact that something appears to be wrong is carefully nutured in her mind until it begins to acquire serious proportions. Symptoms appear. These are often vague and difficult to describe, but they are nonetheless real to her. Is this patient unduly sensitive? Is she neurotic? Perhaps! But she *is* the patient, so it is part of our job to recognize her apprehension and how it came to be. It may all have started as previously indicated, but more than likely a major assist appeared in the form of our failure to explain adequately.

It is not always what we say that does harm. Sometimes it is what we fail to say that nurtures the suspicion of disease. The ability to convey with calm assurance the results of an examination—the finesse which permits use of such words as infection, tumor, and growth, without exciting undue fear—is no common denominator among physicians. Frequently the absence of a tactful conference reflects haste—that devil's handmaiden who seduces us all. The ability to instill confidence, to convey by manner and the spoken word such information as the patient needs to know, is to medicine what the keystone is to the arch. Such skill is sorely lacking in all fields of medicine but its absence works greatest harm among gynecological patients. Since gynecology is an entering wedge in the movement for periodic health examinations, it is especially important that we tighten up on loose talk.

Prominent among the several causes for this predicament is our one-sided pedagogy. I refer more to the neglect of art than to the dominance of science in our medical teaching. Though medical faculties are continually struggling with curricular revisions, they are not attempting to find a place for instruction in the art of communication. With the constant demand for additional hours for the presentation of new scientific material, it is not surprising that art has long since disappeared from most courses. We teach the elements of diagnosis and treatment, but how many hours are devoted to instruction in the skillful conveyance of this information to the patient? The generally casual and even careless approach to this artful aspect of medicine is astounding. We are so harassed trying to keep up with science and medical literature that we have perhaps unavoidably neglected the art. It is time for us to brush up on our exposition to patients and it seems imperative that we commence teaching our medical students and residents how they may avoid pitfalls in this

connection. It is annoying to know that medical students graduate with obvious inadequacy in the use of the spoken and written word. It is equally disturbing to realize that they receive little or no coaching in the art of communication. Possibly it is too much to expect that time for adroit locution be added to already packed curricula. Perhaps this instruction should more properly be part of the residency training program. Whatever the answer, it seems that somewhere along the line there could be a place for it.

In stressing the need for imagination, in affirming the importance of art and improved physician-patient discourse, in extolling brevity of the written word I do not assume the role of a paragon. For in your eyes I may indeed have failed to uphold the very tenets I proclaim. If this be so I shall seek consolation in the thought that you may also perceive the manner of their attainment.

TRANSFER OF MATERIALS ACROSS THE HUMAN PLACENTA*†

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(From the Department of Obstetrics and Gynecology, University of California School of Medicine)

ABOUT thirty years ago the placenta was regarded simply as a semipermeable membrane across which various substances of specified molecular weights diffused in both directions. It was at this time that Grosser[1] developed his morphologic classification of chorioallantoic placentas based upon the number of layers which intervened between the maternal and fetal blood. This served a useful purpose for making certain predictions about the "relative permeability" of placentas, but as pointed out by Amoroso, Wislocki, Dempsey, and others[2] there are many inherent defects in such a classification because the number of effective layers varies in the same species from week to week even in corresponding portions of the same placenta. The electron microscope, furthermore, has revealed significant differences in the nature of the placental barrier from those which were formerly thought to exist.

In the discussion of placental classifications which took place at a conference in 1954,[2] it was felt desirable to attempt the formulation of some other schema. Whether this should be based upon the enzymatic constitution, internal secretions, morphology, rate of senescence, transfer of substances, or some other placental attribute could not be decided. Villee[3] suggested constructing a "profile" for the placenta of each species, listing as many parameters as we wish, and "leaving the ends open for new discoveries."

With respect to the human placenta, a pattern of its enzymatic constitution has been constructed.[4] From a practical standpoint, however, it seems more desirable to develop a schema which would characterize a placenta from a functional standpoint, because it is obvious that intrauterine fetal welfare is dependent upon a certain preciseness in both the qualitative and quantitative selectivity of placental transfer. Such a schema should encompass considerations of the following attributes: (1) the nature and size of materials transported; (2) the relative rates of transfer; (3) the actual mechanisms involved in the transfer; (4) an explanation of inequalities in the distribution of certain substances between maternal and fetal plasmas; (5) the internal secretions of the trophoblast; and, if possible, (6) the primary physiologic significance of any schematic groupings.

*A portion of this work was supported by research grant RG-4702 from the National Institutes of Health, Public Health Service.

†Presented at the Eightieth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 27-29, 1957.

Precise data with respect to all of these points are difficult to find, but enough information about how the human placenta handles certain materials has now accumulated to warrant an attempt to bring these various functions into some orderly arrangement.

The "placental membrane" or "placental barrier" is defined by Wislocki[5] as those tissues of a developing ovum or embryo which are in contact with maternal tissues or fluids at any stage of gestation and which mediate the transfer of substances from the mother to the fetus or in the reverse direction. The trophoblastic layer represents the active parenchyma.

According to this definition, the placental membranes constitute a part of the placental barrier, and this is proper. For the purpose of developing this classification, however, only those mechanisms operating within the placenta and between the two blood streams are being considered. Obviously, this is not the whole story because some materials cross the membranes into the amniotic fluid and thence into the fetus and vice versa. This is certainly true for water and electrolytes, as shown by the fine analysis of the three compartment system by Plentl and his group,[6, 7] and may be true for certain antibodies, as indicated by Brambell.[8] On the other hand, for most materials it appears at this time that transport by way of amniotic fluid plays a relatively minor role.

Some Premises

At this point some general arguments will be presented as an introduction to a more detailed consideration of the various transfer mechanisms.

1. Intact red blood cells and large proteins probably cross almost every human placenta through defects in the barrier, at least in the latter part of pregnancy, but only to a slight and variable degree,[9, 10, 11] and possibly only in the direction of fetus to mother.

2. Therefore, all substances can cross, at least to the same slight extent and in the same direction, provided they are not destroyed or "trapped" during passage.

3. All substances of low molecular weight (e.g., below the range of 350 to 450) can diffuse across the placenta in both directions, provided they are not destroyed during transport. It must be remembered, however, that many seemingly simple substances, such as iron, calcium, phosphorus, magnesium, etc., exist in the blood as complex organic molecules and that others (such as iodine) are attached to large proteins.

4. For any given placenta at any given time, relative rates of passage are dependent upon constants peculiar to the substances to be transported. These "transfer constants" are determined by the size, shape, and electrical charge of the substances, and by the concentration gradients on the two sides of the placental barrier.

5. In addition to diffusion and to the "leakage" of large molecules or particles through the various-sized pores, there are carrier systems for specific foodstuffs such as glucose and amino acids. At certain concentrations, the rate of placental transport by the carrier system may exceed by far the rate of diffusion for the same substances.

6. Some carrier systems require energy and are able to transport materials against the concentration gradient. In such cases, the materials are maintained in an unequal distribution on the two sides of the placental membrane.

7. The distribution of any given substance between mother and fetus, referred to as the C_m/C_f ratio, is complicated by the fact that in the relation of the fetus to its external environment one must deal simultaneously with at least 14 rates of exchange between 6 compartments, as shown by the arrows in Fig. 1. Many of these rates will influence the C_m/C_f ratio. This may be illustrated by the following examples:

a. The absolute rate of transfer in one direction affects distribution. In the case of a very large molecule like fetal hemoglobin, the rate approaches 0 and therefore, the C_m/C_f ratio approaches 0.

b. The actual mechanism of transfer affects the distribution. If the rates from maternal to fetal plasma are dependent upon a carrier system operating against the concentration gradient, as in the case of the natural amino acids, then C_f will always be higher than C_m.

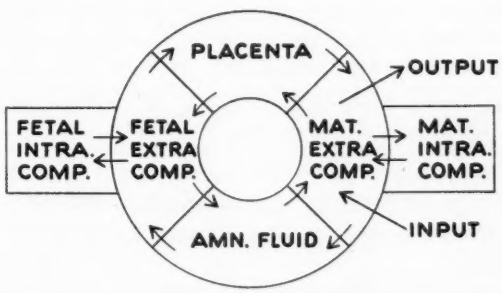


Fig. 1.—Six compartments and the 14 exchanges which may affect the distribution of materials. The fetal and maternal intracellular compartments are shown at the sides of the circle. The fetal and maternal extracellular compartments (which include the respective blood volumes) are shown in relation to the placenta and amniotic fluid. "Output" and "input" represent the activities of the maternal lungs, kidneys, skin, and gastrointestinal tract.

c. The source of the substance, whether it is produced by the mother, the placenta, or the fetus, affects distribution. If, for example, chorionic gonadotrophin is produced by the trophoblast at the maternal surface and the rate of production exceeds the rate of transfer, then this hormone will always be concentrated more in the maternal plasma.

d. Another factor concerns molecular alterations, if any, during transport. A substance such as histamine may enter the placenta but be inactivated by deamination before it can cross.

e. Of greatest importance are the relative rates at which a given substance disappears from maternal and fetal plasma. Rapid falls of plasma concentrations could be due to dilution (the mother is bigger than her fetus), or to excretion by the maternal kidneys; or to differences in the rates of metabolism by mother and fetus; or, if a substance forms a complex with some other molecule, the dissociation constants may be different on the two sides, as in the case of oxygen combining with maternal vs. fetal hemoglobin.

For all these reasons, it can readily be understood why the nature of distribution for any given material does not necessarily indicate the mechanism or the rate of its placental transfer.

8. With rare exceptions, transfer mechanisms operate in both directions. The order of magnitude of the rate, therefore, is not related to the *net* transfer. If a substance should be transported only in one direction (as the case may be for iron), then the absolute rate of transfer and the net transfer become equal. In general, the problem of net transfer over the course of gestation is simply solved by studying the chemical composition of the newborn fetus.

Classification of Functions

When various substances are listed in a descending order relative to the magnitude of their rates of transfer, then the mechanisms of transport appear to fall into four general categories. Surprisingly enough—or perhaps by the design of nature—the substances which comprise each of the four groupings appear to have something in common with respect to their primary physiologic significance for the developing fetus. Of the three attributes, i.e., rate, mechanism, and significance, the last is the most important and will be used, therefore, as a label for each group. Inasmuch as the rates vary so widely from one compound to another or from one period of gestation to another, they can be characterized only in general terms, and the terms selected are the units of time ordinarily used to describe the passage of convenient units of weight.

Group I.—Substances Concerned With the Maintenance of Biochemical Homeostasis or Protection Against Sudden Death.—

Rates of transfer: Measured in milligrams per *second.*

Predominant mechanism of transport: Rapid diffusion.

Under this category are three subdivisions based upon the equality or inequality of distribution.

1. *Equilibrium attained:* The classical examples of substances in this group are water and electrolytes.

Water crosses the placental barrier more rapidly than any other known substance, and in accord with familiar kinetic laws. (Cf. discussion by Chinard.[12] The amount of water transferred in one direction across the placenta from mother to baby is over 500 mg. per second.[6, 7] Obviously, the net transfer is an infinitesimal fraction of the total exchange. At first glance, it would be reasonable to assume that the *net* transfer of water occurs because of Starling's forces, in the same manner as net transfers take place between the water of plasma and the water of the interstitial space of the body as a whole. Because the placental villus capillary pressure is some 20 to 30 mm. Hg above that of the intervillous space, the total osmotic pressure of fetal plasma would have to be 20 to 30 mm. Hg greater than that of maternal plasma, but this does not appear to be true. The mechanism by which water may cross against the pressure gradient is discussed later. Certainly the developing embryo has generous access to all of the water it may require at any time.

Perhaps the most jealously guarded attributes concerned with biochemical homeostasis, or the internal milieu, are the osmolarity of the body fluids and the acid-base balance. Here, the exchange of electrolytes between mother and fetus becomes of paramount importance. The pioneering work of Flexner and his associates[13] has provided us with data on the rates of sodium transfer for the human species. The peak rate of transfer from mother to fetus occurs a month or so before term and is of the order of 1 mg. per second. This is 70 times the

rate per unit of weight of placental tissue that is observed at the tenth week of gestation and this may be due to the progressive thinning of the placental barrier which occurs as pregnancy progresses. Flexner attributes the decline in the last month to the effective diminution of surface by "pathologic" processes such as fibrin deposition.

Several hundred mols of water are exchanged in the same time as 1 mol of sodium. This is necessary in part because each sodium ion is surrounded by many water molecules of hydration. Every molecule that diffuses across the placenta does so at its own rate, and this is determined by the equation of Fick, which, in simplified terms, states that at any given time the rate of transfer is equal to the transfer constant of the substance being considered times the difference in the concentration (or physicochemical activity) of the substance on the two sides of the placental membrane. (For some exceptions to this principle, cf. Danielli.[14])

2. *Unequal distribution due to difference in rates of removal and/or different dissociation constants of complexes formed:* The best example under this subheading is the transfer of oxygen. This problem is admirably summarized by Barron and Meschia,[15] who offer a variant of the Fick equation by saying that:

$$Q = DW\ (P_1 - P_2)$$

where Q is the total quantity of oxygen transferred from mother to fetus per minute; D is the "diffusion coefficient" for oxygen (expressed in milligrams per kilogram of fetus per millimeter of mercury difference in oxygen gas pressure); W is the weight of the fetus; and P_1 and P_2 are the average oxygen pressures in the maternal and fetal blood streams, respectively. P_2 is lower than P_1 by virtue of the rapid withdrawal of oxygen from fetal blood by the fetus, plus the fact that the dissociation of fetal oxyhemoglobin occurs at lower oxygen pressures than the dissociation of adult oxyhemoglobin. From data collected by Romney and co-workers,[16] we learn that for man Q is equal to about 24 ml. per minute; the mean oxygen pressure difference is 37; so that D is about 0.2 (for a 3,200 gram fetus).

For the return of carbon dioxide, the pressure differences are very small so that the diffusion coefficient must be relatively large; that is, carbon dioxide diffuses across the placenta much more readily than oxygen.

It would be interesting to determine whether such compounds as vitamins B_1, B_6, and B_{12} are maintained in fetal plasma at a higher concentration than in maternal plasma because of a firmer binding to fetal enzymes. This would be the reverse of the oxygen-hemoglobin situation. The alternative mechanism would be a specific carrier system operating against the concentration gradient for each of these vitamins.

3. *Unequal distribution due to destruction by the placenta:* The best examples of substances handled in this way, and presumably for the protection of the fetus, are the amines. Compounds such as tyramine, 5-hydroxy-tryptamine (serotonin), and probably epinephrine are quite capable of diffusing across the placenta, but since the latter contains such a high content of monoamine oxidase,[17] ordinary amounts are deaminated during passage and rendered harmless. The same is true of histamine and probably of angiotonin, because of the high content of diamine oxidase and "angiotonase," respectively.[18, 19] In hypertensive disorders mediated by pressor amines (such as pheochromocytoma or acute renal hypertension) it can be understood why the fetus would not share the elevated blood pressure.

Group II.—Substances Concerned Primarily With Fetal Nutrition.—

Rates of transfer: Measured in milligrams per *minute.*

Predominant mechanism of transport: Carrier systems (plus diffusion).

Included in this category are the natural amino acids, from which fetal proteins are synthesized; natural sugars, such as glucose and fructose; and most, if not all, of the water-soluble vitamins. Diffusion of these larger molecules continues to be a mechanism of transfer, but in many instances there appear to be active carrier systems whose rates of transport may exceed the rates of diffusion. There are at least three varieties of transport systems, each resulting in a different type of distribution between maternal and fetal plasmas.

1. *Carrier systems operating equally in both directions:* The calculations of Widdas,[20] based upon data obtained in sheep by Huggett, Warren, and Warren,[21] indicate that diffusion alone cannot account for the transfer of glucose across the placenta. This conclusion was reaffirmed in experiments conducted upon women and monkeys by Chinard and associates.[22]

Carrier molecules are presumed to be oscillating with great rapidity between two of the interfaces of the placental membrane. They pick up glucose molecules waiting at one surface and then release them at the other. The number of saturated carriers going in any one direction is related to the number of riders waiting for transport. When the same number of riders are waiting for transport on each side (i.e., equal concentrations of glucose in the maternal and fetal plasma), then the rates of transfer are equal in both directions. Under these circumstances, it might be surmised that an elevation of maternal blood glucose by intravenous infusion should result in an equality of distribution between the mother and fetus. This does not occur, however, presumably due to two factors. Marked degrees of maternal hyperglycemia may saturate the transport mechanisms. The pedestrian lanes for diffusion are filled and the rapid transport carrier system is overtaxed. The second reason for disequilibrium is the fact that the fetus is constantly utilizing glucose and, even in the steady state, therefore, its glucose level remains lower than that of the mother.

In the case of fructose, the situation is somewhat uncertain. Hagerman and Villee[23] have shown that the human placenta in vitro is capable of transforming glucose into fructose, and that a 500 gram placenta can manufacture about 15 mg. per hour. (This is much less than the placentas of sheep, goats, pigs, deer, horses, and whales are capable of producing.) The concentration of fructose in human fetal blood is low (averaging 5 mg. per cent), but is nevertheless 50 per cent higher than the average value for maternal blood. Isotopically labeled fructose given to the mother will enter the fetal blood[22] and in one experiment saturation of the placental barrier by glucose seemed to interfere with fructose transfer. Based upon this experiment, Chinard and his group concluded that glucose and fructose might ride the same carrier system. They did not, however, explain how the same carrier system can maintain a disequilibrium of the two riders in opposite directions. In the sheep, this problem is discussed in detail by Alexander, Huggett, Nixon, and Widdas.[24]

To this reviewer, the available data are compatible with the concept that in man (a) fructose is produced by the placenta and diffuses equally in both directions, and (b) it disappears more rapidly from maternal blood because of greater dilution and metabolism. The problem might be resolved by making simultaneous measurements of the fructose levels in uterine vein blood and umbilical vein blood, provided that knowledge of blood flow rates could also be obtained. Such an observation does not seem to have been recorded.

2. *Carrier systems operating against the concentration gradient:* It has been known for a long time that the essential amino acids are more concentrated in fetal than in maternal plasma. That this is true for each amino acid has been demonstrated by the chromatographic studies of Crumpler, Dent, and Lindan.[25] Only recently, however, has the existence of a carrier system been demonstrated.[26] In this experiment, two optical isomers of an amino acid,

D- and L-histidine were infused into a maternal vein prior to delivery in such a fashion as to maintain a high and equal concentration of both isomers at the maternal surface of the placental barrier. Infants born about 10 minutes later had an equal concentration of the L-isomer, but a much lower concentration of the unnatural D-isomer. Only after several hours did the C_m/C_f ratio approach unity for both forms. During the initial 10 minutes, when the maternal concentration of histidine was twice as high as the fetal level, the absolute rate of net transfer of L-histidine to the fetus was about 1 mg. per minute. This was 12 times as fast as the rate of net transfer of D-histidine.

Inasmuch as two isomers of the same amino acid should diffuse through the placenta at precisely the same rate, it seems rather evident that there is a carrier system which selects only the natural form for the rapid transit system. Furthermore, these carriers are supplied with enough energy from some source to "carry their riders uphill" until there are more on the fetal side than on the maternal. At a certain point, say twice the concentration in fetal plasma, back diffusion occurs with such rapidity that it competes equally with the carrier system, and a new steady state is achieved. By analogy with the renal tubular cell or the gastrointestinal epithelium, one type of carrier should accept only two or three kinds of amino acids and these compete with each other for transport.

3. *Unequal distribution with resultant molecular alteration during active transport:* An example of this type has been elucidated by Lust, Hagerman, and Villee.[27] The total riboflavin content of fetal blood is 20 per cent higher than that of maternal blood, but the free riboflavin concentration is 300 per cent greater. By a series of experiments, they concluded that a precursor of free riboflavin, flavin adenine dinucleotide, enters the maternal surface but cannot leave the placental membrane. Enzyme splitting then occurs, yielding riboflavin mononucleotide and free riboflavin, both of which now enter the fetal plasma. Similar systems probably exist for the transfer of iron, magnesium, cobalt, and calcium.

In the case of lipids, Popjak[28] has concluded from his own studies on animals and from a review of the literature that all of the fetal phospholipids and most, if not all, of the fetal cholesterol and fatty acids are synthesized by the fetus itself. In the human species, the possibility has not been excluded that some maternal cholesterol and fatty acids diffuse slowly across the placenta, but this is not the major source of fetal fats.

Group III.—Substances Concerned Primarily With Modifications of Fetal Growth and the Maintenance of Pregnancy.—

Rates of transfer: Measured in milligrams per *hour.*

Predominant mechanism of transport: Very slow diffusion of relatively large molecules.

Included under this category are the various steroid and protein hormones produced by the placenta itself or by the maternal endocrine glands. These are relatively large molecules; yet probably all of the steroids and at least some of the protein hormones diffuse very slowly across the placental barrier and undoubtedly serve to modify fetal growth. Maintenance of the pregnancy itself, of course, is dependent upon these hormones.

Grumbach and Werner,[29] using I^{131} labelled thyroxine or tri-iodothyronine in human subjects, demonstrated that small but physiologically significant amounts of both hormones were transmitted to the fetus. The rate of transfer of thyroxine is quite slow, because equilibrium was not even approached until more than 70 hours had passed, but the transfer of tri-iodothyronine was more rapid. The differences may be due to the degree of binding of the two thyroid hormones to specific maternal plasma proteins.

Migeon and co-workers[30] were apparently the first to prove that steroid hormones are transmitted from mother to fetus in the human species. By infusing hydrocortisone into a maternal vein for 30 minutes prior to delivery, the fetal plasma levels of 17-OH-CS were raised from an average of 4 to 77 micrograms per 100 ml. Because fetal concentrations of 17-OH-CS are always lower than maternal levels, the authors concluded that the steroid did not traverse the placenta by simple diffusion. Such a conclusion, however, is not necessarily valid. If the rate of endogenous production by the maternal adrenal is greater than the rate of placental transfer, and the rate of disappearance from the fetal circulation only slightly less than the rate of transfer, then such a steady state of disequilibrium would prevail. Furthermore, one finds that in the authors' cases of elective cesarean section, the 30 minute infusions altered the average C_m/C_f from 6 to 3. If they had continued the infusions for several hours, the ratio might have approached unity.

Chorionic gonadotrophin is produced by the trophoblastic layer of the human placenta. This layer is in immediate contact with maternal plasma, not with fetal plasma, and if this particular protein could not diffuse at all across the basement membrane and the fetal capillary, there would be none in the fetal blood. Bruner[31] has shown, however, that there are appreciable amounts in the fetal circulation, and that the C_m/C_f ratio is between 10 and 20. This high ratio could be explained if chorionic gonadotrophin were near the limits of size, shape, and charge that permit any diffusion at all. That this is true might be surmised from the fact that human chorionic gonadotrophin is cleared by glomerular capillaries very slowly, whereas under normal conditions plasma albumin is not.

Quantitative data with respect to the transfer of maternal insulin, pituitary hormones, parathyroid hormone, etc., are too fragmentary to draw any conclusions at this time.

Group IV.—Substances of Immunologic Importance Only.—

Rates of transfer: Measured in milligrams per *day.*

Mechanisms of transport: Leakage through large pores; droplet transfer by pinocytosis (?).

Into this category fall those molecules, particles, or cells incapable of diffusion through the placental membrane. To travel across, there must be holes sufficiently large to permit passage or the ameboid activities of the membrane itself must participate.

1. *Cellular transfer:* Up to this point we have not considered the difference which exists between the hydrostatic pressure within the fetal capillaries of the placenta and the hydrostatic pressure of the maternal blood in the intervillous space. The first, according to Reynolds,[32] is between 30 and 35 mm. Hg, whereas the pressure in the intervillous space is about the same as that of the amniotic fluid, 5 to 10 mm. Hg between uterine contractions. Even during uterine contractions, the fetal blood pressure rises in a parallel fashion to maintain this gradient of pressure. If it were not so, the chorionic villi would collapse and fetal blood flow through the placenta would cease. The fact that net transfer of the many substances included in Groups I, II, and III takes place against this hydrostatic pressure gradient is a further illustration of the fact that hydrostatic pressure plays a very minor role in controlling rates of diffusion or active transfer. In the case of water, the implication is that the net transfer does not obey Starling's principles since the oncotic pressure of fetal plasma is not 20 to 30 mm. Hg higher than that of maternal plasma. It is probable that the net transfer of water from mother to fetus is "active" in the sense that every substance actively transferred carries with it many water molecules of hydration.

When we come to the question of the transfer of intact red cells through naturally occurring "leaks" in the placental barrier, it seems difficult to believe that such a transfer could occur against the hydrostatic pressure gradient. Studies mentioned earlier[9, 10] indicate that this might occur, but they are hardly conclusive. More impressive is the demonstration of large amounts (over 2 per cent) of fetal hemoglobin in some 5 per cent of all obstetrical patients. Such a leakage of fetal blood into the intervillous space may be of sufficiently serious degree to cause marked anemia in the fetus.[11] In one case which we observed recently, the process evidently caused classical hydrops fetalis (except for a small spleen) with death in utero. The story of antibody responses by the mother to this infusion of fetal cells is too well known to recount here. The chief argument at this point is that red cell traffic must be predominately if not wholly in one direction. This premise would also explain why the blood of a fetus of a leukemic mother does not contain leukemic cells.

2. Pinocytosis: There is a mechanism by which large molecules, such as maternal plasma proteins, could be transported against the hydrostatic pressure gradient. This process, discovered by Palade and applied to the problem of human placenta by Dempsey[33] is one in which "the basal endothelial membrane rounds up into little vesicles, which apparently migrate through the cytoplasm to discharge their contents through the plasma membrane on the opposite side." The surface of the syncytium, as revealed by the electron microscope, consists of myriads of microvilli which are presumed to be in constant motion during life, engulfing tiny droplets of fluid and drinking them into the cytoplasm. Whether the droplets are discharged into the fetal circulation or not remains to be proved. In any case, the quantities of substances transferred in such a manner are probably too small to have any nutritional significance, but might be important from an immunologic standpoint.

Summary

A tentative classification of transport mechanisms across the human placenta is proposed, based upon (a) the primary physiologic significance of the substances transferred, (b) the relative rates of transfer, (c) the actual mechanisms of transport, and (d) the equality or inequality of distribution. The proposed schema, together with some examples, is as follows:

Group I.—Substances concerned with the maintenance of biochemical homeostasis or protection against sudden fetal death.

Rates of transfer: Milligrams per second.

Predominant mechanism of transport: Rapid diffusion.

1. Equilibrium attained.
   Examples: Water and electrolytes.
2. Unequal distribution due to differences in rates of removal and/or different disassociation constants of complexes formed.
   Examples: Oxygen and carbon dioxide.
3. Unequal distribution due to destruction by the placenta.
   Example: Amines.

Group II.—Substances concerned primarily with fetal nutrition.

Rates of transfer: Measured in milligrams per minute.

Predominant mechanism of transport: Carrier systems (plus diffusion).

1. Carrier systems operating equally in both directions.
   Example: Glucose.
2. Carrier systems operating against the concentration gradient.
   Example: Amino acids.
3. Unequal distribution with resultant molecular alteration during active transport.
   Example: Riboflavin.

Group III.—Substances concerned primarily with modifications of fetal growth and the maintenance of pregnancy.

Rates of transfer: Measured in milligrams per hour.

Predominant mechanism: Slow diffusion.

Examples: Steroid and protein hormones of maternal or placental origin.

Group IV.—Substances of immunologic importance only.

Rates of transfer: Measured in milligrams per day.

Mechanisms of transport: Leakage through large pores; droplet transfer by pinocytosis(?).

1. Cell transfer.
   Example: Red blood cells.
2. Pinocytosis (?).
   Example: Plasma proteins.

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References

1. Grosser, O.: Fruhentwicklung, Eihautbildung und Placentation des Menschen und der Saugetiere, Munich, 1927, J. F. Bergmann.
2. Flexner, L. B., editor: Gestation, Transactions of the First Conference, New York, 1954, Josiah Macy, Jr., Foundation, pp. 119-224.
3. Villee, C. A.: In Flexner, L. B., editor: Gestation, Transactions of the First Conference, New York, 1954, Josiah Macy, Jr., Foundation, p. 215.
4. Page, E. W., and Glendening, M. B.: In Flexner, L. B., editor: Gestation, Transactions of the First Conference, New York, 1954, Josiah Macy, Jr., Foundation, pp. 225-229.
5. Wislocki, G. B.: In Flexner, L. B., editor: Gestation, Transactions of the First Conference, New York, 1954, Josiah Macy, Jr., Foundation, p. 9.
6. Gray, M. J., Neslen, E. D., and Plentl, A. A.: Proc. Soc. Exper. Biol. & Med. **92**: 463, 1956.
7. Hutchinson, D. L., Hunter, C. B., Neslen, E. D., and Plentl, A. A.: Surg., Gynec. & Obst. **100**: 391, 1955.
8. Brambell, F. W. R.: Cold Spring Harbor Symposia on Quantitative Biology, Vol. XIX, 1954, pp. 71-81.
9. Hedenstedt, S., and Naeslund, J.: Acta med. scandinav., supp. 170, p. 126, 1946.
10. Mengert, W. F., Rights, C. S., Bates, C. R., Jr., Reid, A. F., Wolf, G. R., and Nabors, G. C.: Am. J. Obst. & Gynec. **69**: 678, 1955.
11. Bromberg, Y. M., Salzberger, M., and Abrahamov, A.: Obst. & Gynec. **7**: 672, 1956.
12. Chinard, F. P.: Cold Spring Harbor Symposium on Quantitative Biology, Vol. XIX, 1954, pp. 209-213.
13. Flexner, L. B., Cowie, D. B., Hellman, L. M., Wilde, W. S., and Vosburgh, G. J.: Am. J. Obst. & Gynec. **55**: 469, 1948.
14. Danielli, J. F.: In Davson, H., and Danielli, F. J.: The Permeability of Natural Membranes, ed. 2, Cambridge, 1952, Cambridge University Press, Appendix A.

15. Barron, D. H., and Meschia, G.: Cold Spring Harbor Symposia on Quantitative Biology, Vol. XIX, 1954, pp. 93-101.
16. Romney, S. L., Reid, D. E., Metcalf, J., and Burwell, C. S.: AM. J. OBST. & GYNEC. **70**: 791, 1955.
17. Luschinsky, H. L., and Singher, H. O.: Arch. Biochem. **19**: 95, 1948.
18. Swanberg, H.: Acta physiol. scandinav., supp. 79, **23**: 1, 1950.
19. Page, E. W.: Unpublished data.
20. Widdas, W. F.: J. Physiol. **118**: 23, 1952.
21. Huggett, A. St. G., Warren, F. L., and Warren, N. V.: J. Physiol. **113**: 258, 1951.
22. Chinard, F. P., Danesino, V., Hartman, W. L., Huggett, A. St. G., Paul, W., and Reynolds, S. R. M.: J. Physiol. **132**: 289, 1956.
23. Hagerman, D. D., and Villee, C. A.: J. Clin. Invest. **31**: 911, 1952.
24. Alexander, D. P., Huggett, A. St. G., Nixon, D. A., and Widdas, W. F.: J. Physiol. **129**: 367, 1955.
25. Crumpler, H. R., Dent, C. E., and Lindan, O.: Biochem. J. **47**: 223, 1950.
26. Page, E. W., Glendening, M. B., Margolis, A. J., and Harper, H. A.: AM. J. OBST. & GYNEC. **73**: 589, 1957.
27. Lust, J. E., Hagerman, D. D., and Villee, C. A.: J. Clin. Invest. **33**: 38, 1954.
28. Popjak, G.: Cold Spring Harbor Symposia on Quantitative Biology, Vol. XIX, 1954, pp. 200-208.
29. Grumbach, M. M., and Werner, S. C.: J. Clin. Endocrinol. **16**: 1392, 1956.
30. Migeon, C. J., Prystowsky, H., Grumbach, M. M., and Byron, M. C.: J. Clin. Invest. **35**: 488, 1956.
31. Bruner, J. A.: J. Clin. Endocrinol. **11**: 360, 1951.
32. Reynolds, S. R. M.: In Villee, C. A., editor: Gestation, Transactions of the Second Conference, New York, 1956, Josiah Macy, Jr., Foundation, p. 223.
33. Dempsey, E. W.: In Flexner, L. B., editor: Gestation, Transactions of the First Conference, New York, 1954, Josiah Macy, Jr., Foundation, pp. 36-42.

Discussion

DR. ROBERT A. ROSS, Chapel Hill, N. C.—In this presentation a placenta scheme is characterized from a functional standpoint with emphasis and explanation of transfer of materials across the human placenta. Only those mechanisms operating within the placenta and between the fetal and maternal blood stream are being considered, though substances do cross the membranes to and from the amniotic fluid and fetus, notably water and electrolytes and perhaps antibodies.

From accumulating evidence it appears that any substance in either circulation might at some time and in varying degrees during pregnancy reach the other system, though some might be destroyed, altered, or delayed in passage. Many and varied mechanisms as electrical charge, energy, concentration, carrier systems, diffusion, pinocytosis, and leakage aid in this interchange.

The essayist has listed the substance in four groups and finds three common attributes having to do with the maintenance of pregnancy and the welfare of the fetus, the most important of which is the significance of the substance in carrying out this biologic obligation.

At the present time we are studying the histology of both the early and late placenta, tracing certain vitamins from mother to fetus, the maternal and fetal blood levels and placental content of various analgesic and anesthetic drugs, and blood clotting factors in mother, fetus, amniotic fluid, and placenta.

The juvenile diabetic patient especially is a remarkable person and her pregnancies are likely to be. The placenta can illustrate "compressed" geriatrics and probably the placenta in the diabetic can add to our general knowledge. The utilization of vitamins, considered as "exogenous" hormones, the raw material, is being investigated. Our other present study embraces the clotting mechanism in both infant and mother, checking the finding of hyperfibrinogenemia in the mother at term and hypofibrinogenemia in the infant. Something much more basic than the fibrinogen level must contain the answer.

There is a full gamut from placenta accreta to hydatiform mole; there is a noteworthy parallel between them. The placenta and cord are on the side of the fetus and by vascular shunt, synthesis, storage, and deamination and alteration do protect it. However, it is a two-edged affair. It can allow sensitization of the mother with subsequent death of the fetus.

The fetus itself can produce placental infarcts which in turn can imperil both itself and the mother. The acute bleeding associated with abnormal position and behavior are all too familiar. Unrestrained growth in its early stage and departure from normal in its later life lead to the bizarre and fatal chorionepithelioma, and the "senescent" placenta does jeopardize the fetus.

Members of this Society have contributed greatly to our knowledge of the placenta. McCord in his long and careful review of the syphilitic placenta had later support from Montgomery. Bartholomew and his co-workers gave histologic, chemical, and bacteriologic information on the placenta in the toxemias of pregnancy, and recorded an obvious phenomenon that had not been adequately studied—marginal sinus rupture. Eastman, Hellman, and others investigated histology, oxygenation, and other interchanges. At present, Hertig, Page, Taylor, Barnes, and others are busy with the chemistry and function of the placenta. This must be an "all hands" job if the rough facets are smoothed, certain findings rearranged, and incomplete segments filled in.

As a member of the Chorionepithelioma Registry of the American Association of Obstetricians and Gynecologists, I have learned to respect this important organ and am certain that the incinerator is not the proper initial repository for abortuses and placentas.

DR. E. STEWART TAYLOR, Denver, Colo.—Some of my students have indicated a disinterest in the physiology of the fetal membranes and have turned their interest with more enthusiasm to the mechanical or surgical aspects of obstetrics. I try to guide them back to the physiologic concepts of reproduction by gently reminding them that a knowledge of placental physiology is the "hallmark" that distinguishes an obstetrician from a midwife.

Dr. Page's functional classification of the placenta in some ways parallels morphologic changes that occur in the placenta.

Group I.—His first group in the functional classification is concerned with maintenance of biochemical homeostasis or protection against fetal death. In its purest form, this group is exemplified by the embryo during its first eight days. During this period the embryo is nourished by water, electrolytes, oxygen, carbon dioxide, and possibly other elements. This primitive activity is maintained but improved until term in normal pregnancy. For example, Flexner and his group have shown that the rate of transfer of sodium across a given unit of human placenta increases rapidly as the placenta matures.

Group II.—The second functional group becomes operational when the embryo develops from the histotroph to the hemotroph stage. The specialized cells of the chorion assume many functions. At this same period, rapid growth of the embryo occurs. The chorion contributes to the transport of glucose and amino acids from maternal to fetal blood. Placental enzymes also alter molecular structure of such essentials as the precursors of free riboflavin. In the process of maturing, the villi become smaller, the total absorptive surface of the placenta increases, and Langhans' layer tends to disappear, and the villi become more highly vascularized.

Group III.—Next is the group which includes the large molecules, such as the steroid and protein hormones. These are compounds that seem to have little opportunity to pass from the mother to the fetus until certain morphologic changes occur in the placenta. Until after the seventh gestational month, very little estrogen enters the fetal circulation. Maternal antibodies are also usually unable to reach the fetal circulation until about the seventh gestational month.

Recent developments, initiated through studies of interaction of cells with viruses, have produced suggestions which may find applicability to the problem of permeability of specific molecules across biologic membranes. It has been shown that a bacteriophage attaches to a sensitive host cell by a reaction which, in its first stages at least, is purely electrostatic. Within a very short time after this initial interaction, a wave of permeability increase sweeps over the host cell, and metabolites of different kinds from inside the cell leak out freely from the membrane. Shortly thereafter a wave of refractoriness sets in, and this leakage stops. Now attachment of a second virus of this same kind to this host cell no

longer triggers a new increase in cell permeability, regardless of where on the cell the second virus attaches. However, if a virus of an unrelated kind now is permitted to attach to this same cell, another new wave of permeability increase can be elicited.

On the basis of results like these, it has been postulated that cell walls are crisscrossed by electrochemical networks whose stimulation by specific molecules can result in fairly rapid changes in permeability. The virus is pictured in this process as simply availing itself of already existing permeability mechanisms, which it utilizes in order to inject its own nucleic acid past the cell wall into the cytoplasm. Presumably, transport of other large and small molecules may be mediated by specific electrochemical receptor mosaics on the membrane.

DR. ARTHUR T. HERTIG, Boston, Mass.—In listening to Dr. Page delineate the mechanism of transfer of glucose across the "placental barrier," I was intrigued by the fact that no mention was made of glycogen. I wonder whether this intermediate substance plays any part in the transfer of glucose because in the early ovum there is definite evidence of a large amount of glycogen and some glycoprotein in the syncytiotrophoblast, at least in the 13 day ovum. The histochemical aspects of this ovum were presented in abstract form before the American Association of Anatomists in Baltimore on April 17, 1957. Among other things we showed an enormous amount of glycogen in the syncytiotrophoblastic masses in this early villous ovum. I wonder, whether, in a sense, this primitive syncytiotrophoblast acts somewhat in the form of a liver before the fetus actually gets a liver of its own.

The next point was the beautiful diagram of pinocytosis and phagocytosis of these small particles. In the 12 day ovum, there is active evidence of phagocytosis by the primitive syncytiotrophoblast of what appears morphologically to be maternal red cells. It thus occurred to me that perhaps one would not have to rely entirely upon the mechanical leakage of maternal red cells across the "placental barrier" to account for the isoimmunization that results in hydrops fetalis. I wonder if it could be shown by the Coons fluorescent technique, which localizes the antigen antibody reaction, that the antigen may well be carried across the "placental barrier" with this phagocytosed maternal erythrocyte and hence sensitize the fetus by that mechanism rather than getting across purely mechanically.

DR. EDWARD C. HUGHES, Syracuse, N. Y.—Dr. Hertig has remarked concerning the deposition of glycogen in the early chorion. In connection with his remarks it has been our good fortune to have several early ova which we have studied for glycogen and alkaline phosphatase deposition. The Langhans' cells of the chorionic villi seem to deposit a large amount of glycogen but there is a small amount of phosphatase found in the syncytial cells of the chorion. During this time of gestation the fetal liver contains no glycogen but seems to be more of a blood-forming organ. Some time in the middle portion of gestation, after the placenta is completely formed, its function changes from one of storage of carbohydrate to one of transfer. The Langhans' cells disappear mostly and there is no more sugar found in the remaining cells. The chorionic villi adapt themselves for transfer of material from the decidua to the fetus and the fetal liver begins to store large amounts of sugar as glycogen. Interestingly enough, in several cases of diabetes and toxemia of pregnancy the placenta seems to revert back to an earlier form or it takes on a different function. Then again we find the storage of some material which seems to resemble glycogen. Apparently there is a change in the function of the chorion in the midportion of gestation.

DR. CHARLES A. BEHNEY, Lansing, Mich.—Nine months ago the Maternal and Child Health Division of the Michigan Department of Health, at the suggestion of Dr. Norman Miller, began a prospective study of the transport of the virus of German measles across the placenta and its effect on the human fetus. In this short space of time we were able to collect 75 cases in which pregnancy was complicated by rubella, 55 of which were diagnosed by physicians.

Embryologic defects were recognized at, or shortly after, birth in only 6 instances. The remainder of cases in which the complication occurred will be followed up in order

to learn of anomalies that may be recognized later in infants apparently normal during the neonatal period. There were 4 spontaneous abortions. We have learned of no therapeutic abortions performed during the past year because of a pregnancy complicated by rubella.

TABLE I. EMBRYOLOGIC DAMAGE IN 75 PREGNANCIES COMPLICATED BY RUBELLA

Number of cases reported	75
Number of cases physician diagnosed	55
Congenital defects	6
Percentage of congenital defects	8
Spontaneous abortions	4

TABLE II. CONGENITAL DEFECTS BY TRIMESTER IN WHICH RUBELLA COMPLICATED THE PREGNANCY

	NO. OF CASES OF RUBELLA	CASES DIAGNOSED BY PHYSICIAN	NOT DIAGNOSED	DEFECTS
First Trimester.—				
	35	1		Hypospadias
		1		Syndactylism, calcaneovalgus
			1	Congenital cataract, congenital heart disease
		1		Congenital cataracts, congenital heart disease, hypospadias, undescended testicle, equinovalgus
		1		Macerated stillborn infant
Second Trimester.—				
	24	1		Microphthalmus
Third Trimester.—				
	10			None
Not Reported.—				
	6			None
Total	75			

DR. PAGE (Closing).—Certainly it appears that almost anything can cross the placenta, at least to a slight degree, and this calls for a shift of emphasis in our thinking. The crucial question is no longer, "Can A or B cross the human placenta?" but rather, "How rapidly is it transferred and what is its physiologic significance, if any?"

The influence of certain diseases on placental function has been raised. It has been noted that in severe pre-eclampsia the ability of the placenta to concentrate amino acids on the fetal side is lost. To me, this suggests that there is a loss or impairment of the active carrier systems. Perhaps, this, rather than an impairment of oxygen transfer, leads to the slowing or cessation of fetal growth which is so often associated with toxemia. The higher the concentration of essential amino acids in fetal plasma, the more rapid is protein synthesis. When the placenta is reduced by disease to a simple "filter," the rate of protein synthesis, hence growth, may be slowed.

Dr. Hertig raised a point about glycogen formation. This may be a phenomenon quite separate from the rate of glucose transfer itself, and I do not know the factors which control it. The parallel rises and falls of maternal and fetal glucose are most likely quite independent of the glycogen problem. As for the phagocytosis of red blood cells, I have been told that this has never been observed in the human placenta after the first month and therefore concluded that it could not be concerned with red cell transfer.

Dr. Ross made a plea for not discarding the placenta too rapidly without pausing to reflect upon its potentialities. I wish to reinforce that plea and add:

Don't make mirth
Of the afterbirth!

OVARIAN FUNCTION AFTER THE MENOPAUSE*

CLYDE L. RANDALL, M.D., PAUL K. BIRTCH, M.D., AND JOHN L. HARKINS, M.D., BUFFALO, N. Y.

(From the University of Buffalo School of Medicine)

FOR years references have been made to the probability of ovarian function after the menopause. Little real effort has been made, however, to establish a basis for belief that the human ovary continues an essential function after cessation of the menstrual cycle.

Material

In an effort to learn something of the evidences of estrogen effect in the vaginal smears following cessation of the menstrual cycle, the cytology of postmenopausal women examined in the office has recently been reviewed. Included in this study are the smears of 183 women evaluated for estrogen effect one or more years following hysterectomy, and the smears of 112 others observed for evidences of estrogen effect one or more years following castration by removal of the ovaries or irradiation. The smears of 1,473 women have been evaluated for estrogenic effect one or more years following the spontaneous cessation of their periods, a total of 1,768 patients. Since July, 1949, the smears taken primarily as a cancer detection measure at the time of the more or less routine pelvic examination of 15,000 patients seen in one office have also been evaluated for estrogen effect. The 1,768 patients whose smears provide the basis of this report were selected because they had experienced no menstruation for longer than one year and had received no estrogenic therapy for 6 or more months prior to the date of the smear incorporated in these data.

Results

Spontaneous Cessation of Menstruation.—

A deficiency of estrogenic effect was noted in the smears of 60 women observed one to 2 years following spontaneous cessation of menstruation, in 120 women whose smears were evaluated between 2 and 5 years following spontaneous cessation of their periods, in 163 women whose smears were evaluated 5 to 10 years after spontaneous cessation of their periods, in 153 women whose smears were evaluated 10 to 15 years following spontaneous cessation of their periods, and in 165 women whose smears were evaluated more than 15 years after the menopause. Thus, in a total of 661 cases (44.8 per cent of the series) a deficiency of estrogen effect was indicated.

A persistence of estrogenic effect was noted in the smears of 171 women whose cytology was evaluated between one and 2 years following spontaneous cessation of menstruation, in 212 women whose smears were evaluated 2 to 5 years following spontaneous cessation of their periods, in 200 women whose smears were evaluated 5 to 10 years following spontaneous cessation of their

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periods, in 108 others whose smears were evaluated 10 to 15 years following spontaneous cessation of their periods, and in 121 women whose smears were evaluated more than 15 years after the menopause. A persistence of estrogen effect was thus noted in 812, or 55.2 per cent, of the women studied in this series.

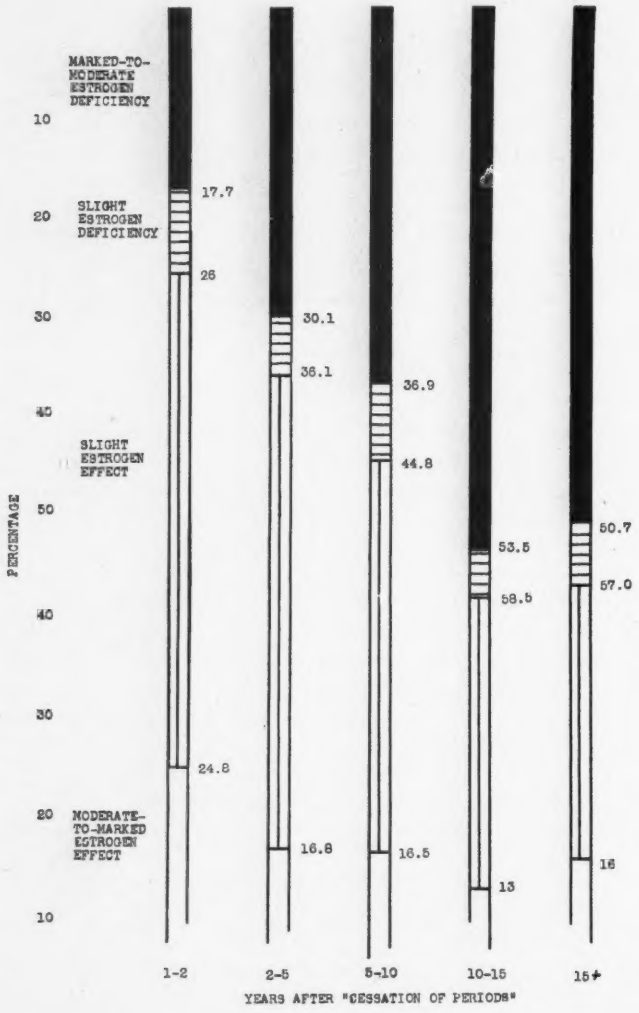


Fig. 1.

Observations to date have been summarized as follows (Fig. 1):

Of the women whose vaginal smears were evaluated for estrogen effect one to 2 years following spontaneous cessation of their periods, as the first column indicates, 17.7 per cent suggested a moderate-to-marked estrogen deficiency and an additional 8.2 per cent revealed a slight estrogen deficiency. The smears of 24.8 per cent of this group revealed the persistence of a moderate-to-marked estrogen effect, whereas the remaining 50 per cent suggested the persistence of only a slight estrogen effect.

Of the women whose vaginal smears were evaluated 2 to 5 years following spontaneous cessation of their periods, 30.1 per cent revealed a marked-to-moderate deficiency of estrogen and an additional 6 per cent revealed a slight

deficiency of estrogen. The smears of 16.8 per cent of this group indicated the persistence of a moderate-to-marked evidence of estrogenic effect, whereas those of the remaining 46.9 per cent indicated only slight evidence of the persistence of estrogen.

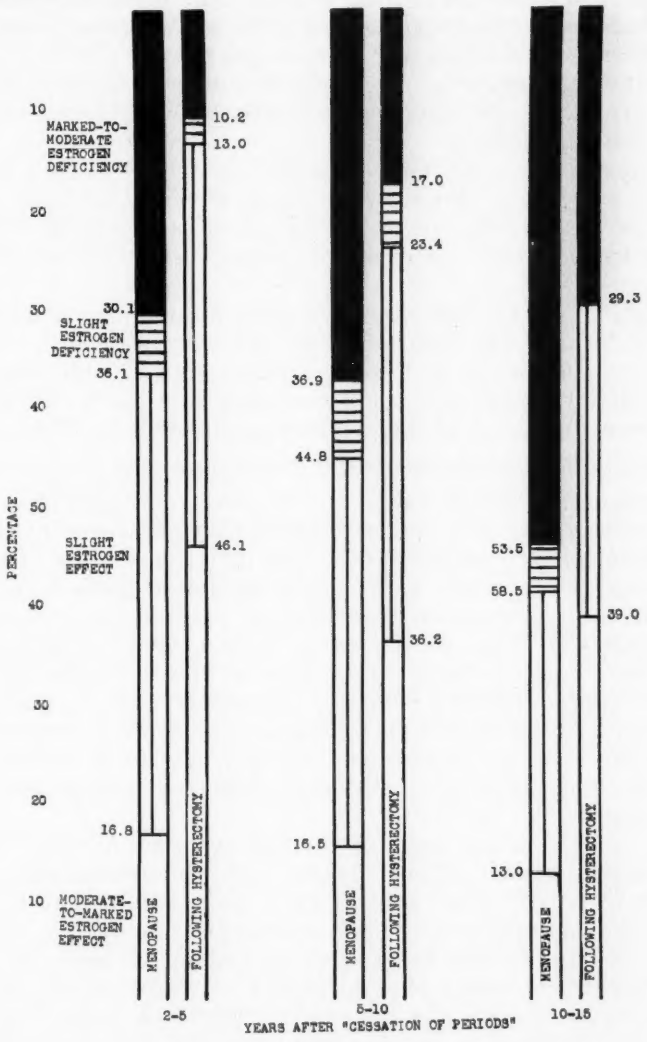


Fig. 2.

Of the women whose smears were evaluated 5 to 10 years after spontaneous cessation of their periods, 36.9 per cent showed a marked-to-moderate deficiency of estrogen and an additional 7.9 per cent showed but slight evidence of estrogen deficiency. The smears of 16.5 per cent showed moderate-to-marked evidence of the persistence of an estrogen effect, whereas those of the remaining 38.6 per cent showed but slight evidence of persistent estrogen effect.

Fifty-three and five-tenths per cent of the women whose vaginal smears were evaluated 10 to 15 years following spontaneous cessation of their periods, showed marked-to-moderate evidence of estrogen deficiency and an additional 5 per cent showed but slight evidence of estrogen deficiency. The smears of

13.0 per cent revealed moderate-to-marked evidence of the persistence of estrogen effect, whereas those of the remaining 28.7 per cent revealed but slight evidence of such persistent estrogen effect.

Of the women whose vaginal smears were evaluated 15 or more years following spontaneous cessation of their periods, 50.7 per cent revealed a marked-to-moderate deficiency of estrogen effect and an additional 6.3 per cent showed but slight evidence of a deficiency of estrogen effect. The smears of 16.0 per cent of this group suggested moderate-to-marked estrogen effect, whereas those of the remaining 26.2 per cent showed but slight evidence of the persistence of an estrogen effect.

It is interesting to note, among the group whose smears were evaluated more than 15 years after cessation of their periods, that the percentage of women who showed a deficiency of estrogen effect was less than that of the women whose smears were evaluated between 10 and 15 years after the menopause.

A number of factors must influence these figures and consideration of the possibilities is beyond the limits of the present discussion. There is some reason to suspect, however, that women whose smears indicated a marked-to-moderate deficiency of estrogen may be dying at a more rapid rate than are women who show evidences of the persistence of estrogen effect.

Comparison: Posthysterectomy and Postmenopausal Series.—

The smears of 183 women taken one or more years following hysterectomy when the ovaries were not removed suggest that preserved ovaries often continue to function and for significantly long periods of time (Fig. 2). Of 332 women examined 2 to 5 years following cessation of periods, 36.1 per cent of those who had a normal menopause showed varying degrees of estrogen deficiency, whereas only 5, or 13 per cent, of 39 patients followed 2 to 5 years following hysterectomy showed appreciable evidence of ovarian deficiency.

Five to 10 years following cessation of periods, 44.8 per cent of 363 women examined after an apparently normal menopause showed evidences of ovarian deficiency, whereas the smears of only 23.4 per cent of 47 women examined at a time equally long after hysterectomy suggested comparable evidences of estrogen deficiency.

The smears of 58.5 per cent of the 261 women followed 10 to 15 years after spontaneous cessation of periods reveiled evidences of estrogen deficiency but the smears of only 29.3 per cent of 41 women examined 10 to 15 years after hysterectomy showed evidences of estrogen deficiency.

The data in Fig. 2 seem to suggest that about 21 per cent fewer women will show cytologic evidences of a deficiency of estrogen 5 to 10 years following hysterectomy, if the ovaries have been preserved, than those followed for an equal length of time after spontaneous cessation of their periods.

Among those examined 10 to 15 years after hysterectomy with preservation of the ovaries, a demonstrable deficiency of estrogenic effect was thus evident in approximately 30 per cent fewer patients than in those examined an equal length of time following a spontaneous menopause.

Comparison: Posthysterectomy and Postcastration Series.—

Fig. 3 excludes data regarding the women examined after spontaneous cessation of their periods. Here the frequency with which estrogen deficiency was demonstrable at varying lengths of time after castration, whether by irradiation or removal of the ovaries, is compared with the frequency with which ovarian deficiency can be expected to develop within an equal length of time following hysterectomy when ovarian function has been preserved. It will be noted within each of the groups considered that evidence of ovarian

deficiency has been noted in approximately 30 per cent fewer women when menstruation stopped after hysterectomy as compared to the frequency of estrogen deficiency among women whose menstruation stopped following castration. These data seem to suggest that approximately 30 per cent more women subjected to hysterectomy would experience the effects of ovarian deficiency if all were castrated by removal of the ovaries whenever hysterectomy was indicated.

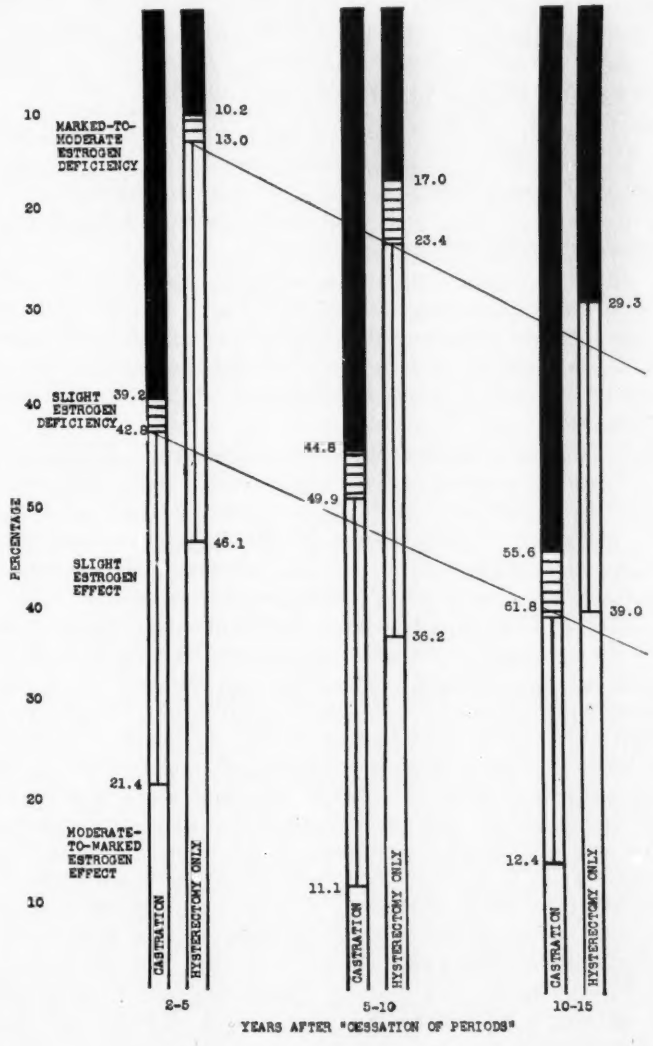


Fig. 3.

Relationship of Estrogen Deficiency, Hypertension, and Atherosclerosis

In an effort to learn whether, in the Buffalo area, removal of the ovaries seems to be associated with the development of a significant degree of arteriosclerosis in younger women, Harkins and Frankel have recently studied autopsy records of the Buffalo General Hospital. The protocols of 3,100 cases were reviewed. The records of 37 women over 35 years of age at the time of their deaths, castrated 2 or more years preceding their deaths, have suggested

an incidence of atherosclerotic lesions that has been compared with the vascular changes noted among 100 controls. (Controls were women over 35 years of age who showed apparently normal ovaries at the time of autopsy.)

Wuest and associates[12] have emphasized that women whose ovaries had been removed at a relatively early age develop a degree of atherosclerosis not seen among normal women until such controls are 20 or more years older than the castrates. Harkins and Frankel noted, among the women who died before their fiftieth year, that 4 of 23 regarded as controls (17.4 per cent) had died of vascular disease. We might, therefore, regard this as evidence that not more than 20 per cent of women not castrated should be expected to die of cardiovascular disease before 50 years of age.

On the other hand, of 37 women who came to autopsy after bilateral oophorectomy, 5 died before their fiftieth year and in 4 of those 5, or 80 per cent of the castrated women, death had been due to vascular disease. These castrated women were young, yet atherosclerosis and hypertension seemed to have contributed significantly to their deaths.

Reviewing the records of patients examined during the course of the office practice of gynecology, we have also noted a tendency toward development of arteriosclerotic disease and hypertension more frequently among women whose smears indicate a deficiency of estrogens at a relatively younger age. In this study all readings of 150/90 and higher were regarded as evidence of hypertension.

Of 163 women whose smears indicated a deficiency of estrogen 15 or more years after spontaneous cessation of their periods, 63.2 per cent had hypertension. Master[6] has reported that 67.7 per cent of all women 60 to 69 years of age have blood pressure readings of 150/90 or higher, therefore, the 63.2 per cent incidence of hypertension in women who show a deficiency of estrogen 15 years after spontaneous cessation of their periods seems of little significance. We also noted, among 115 women whose vaginal smears indicated an estrogen effect, persistent 15 or more years after spontaneous cessation of their periods, that the incidence of hypertension was 59.1 per cent. This figure, noticeably lower than Master's estimated 67.7 per cent probability of hypertension among all women within this age group, is suggestive, and differences were striking among younger women observed soon after cessation of their periods. Master's figures indicate, among women 40 to 49 years of age, a probable incidence of 32 per cent hypertension. We have observed that blood pressures of 150/90 and higher were evident in 37.5 per cent of 48 women whose vaginal smears indicated a complete lack of estrogenic effect between one and 2 years after spontaneous cessation of their periods. This is a somewhat higher figure than Master's 32 per cent probability of hypertension among women 40 to 49 years of age. More significant, however, is the fact that we have found hypertension in only 13.2 per cent of 111 women whose vaginal smears indicated moderate-to-marked estrogen effect between one and 2 years after spontaneous cessation of their periods.

Admittedly few cases are involved, but among women who show an "estrogen deficiency" type of smear 2 years after cessation of their periods, our data seem to suggest that we might expect to find a greater number of younger women with hypertension than the average incidence of vascular disease at this age would lead us to expect. On the other hand, when smears suggest persistence of estrogen effect within 2 years after spontaneous cessation of menstruation, the incidence of mild hypertension seems to be only one third to one fourth of the over-all or average figure Master's data would lead us to expect.

Comment

We have observed cytologic evidences of estrogen effect (in cervical smears as taken by the Ayre spatula) among women examined at varying lengths of time after (a) spontaneous cessation of menstruation (b) hysterectomy when the ovaries were preserved, and (c) castration. The smears of a majority of the women examined indicate the persistence of estrogen effect for more than 15 years after hysterectomy. This at least suggests that, when the ovaries are preserved, they *may* continue to function for years after hysterectomy. The proportion of women whose smears indicate the persistence of estrogen effect for years after removal of both ovaries suggests, however, that tissues other than the ovary may be important sources of the estrogens whose effect is reflected in the smears. After the ovaries have been removed there seems but little evidence, however, to suggest that the estrogens derived from extraovarian sources may thereafter be provided in larger amounts to meet the deficiency due to oophorectomy.

Livingston[5] has reported the results of an investigation carried out to determine the length of survival and mode of function of the ovaries following hysterectomy. He quotes Rubenstein and Duncan as having demonstrated in 1941 that there is a close correlation between the pattern of the vaginal smear and the level of urinary estrogen excretion. Livingston believes, though his study is based upon only 37 patients who underwent repair of prolapse and 23 more who had abdominal hysterectomy, that his results do indicate such a close correlation between the vaginal smear and the endometrium during reproductive life and after the menopause.

Livingston also described a review of abdominal hysterectomies with conservation of ovarian tissue. Three hundred and fifty-three of the hysterectomies had been performed on women under 45 years of age. Summarizing his observations, Livingston concluded that the performance of hysterectomy with conservation of the ovaries does nothing to hasten the onset of menopausal symptoms or the development of atrophic changes.

The production of estrogens after the menopause has recently been discussed by Struthers.[10] Apparently a majority of the British investigators have also considered that the production and utilization of estrogens were of little or no significance after the menopause. Struthers suggests, however, that opinions are changing; many now believe that in at least some women estrogenic effects are of importance long after the menopause.

Struthers employed vaginal smears as a means of estrogen determination, and quoted Aeppli and Rosenmund as having suggested that the cytologic method has evident practical advantages over the biological assays of Allen and Doisy. The smears for Struthers' study were made by the use of a spatula, stroked firmly down the upper third of the anterior wall of the vagina. Staining was employed as described by Papanicolaou in 1948.

Considering the probability that estrogen production might fluctuate after the menopause, and that one test of each patient might be misleading, Struthers reports that 40 unselected postmenopausal patients had smears taken at intervals of 4 to 8 weeks. When the smears thus taken on two occasions were compared, however, assays on the same patients were reported to show variations approximating only 2.6 per cent.

Summarizing observation of a total of 353 women examined, Struthers concluded that in 53.2 per cent considerable estrogenic activity was evident after the menopause, that an additional 26.6 per cent indicated a persistence of some estrogen effect, and that no estrogen was demonstrable in only 20.1 per cent of the women examined.

Observations are also summarized which led Struthers to believe that the amount of estrogen produced by the postmenopausal ovary might be insignificant. In an effort to determine whether the adrenals were the source of a significant proportion of the estrogen produced by the postmenopausal woman, Struthers had examined the vaginal smears of women whose ovaries and adrenals had been removed. Eight such patients became available in Struthers' group, but one died within 24 hours after the adrenalectomy. In 3 patients there was no change in the estrogen level, in a fourth there was a slight reduction, in the remaining 3 the cytology suggested that the estrogen level had remained unchanged. At the time of this report, Struthers suggested that, if any conclusions could be drawn from so small a series, his observations seemed to indicate that the adrenals were obviously not the only extraovarian source of postmenopausal estrogen.

Strong and associates,[9] in a study of hormone excretion after bilateral adrenalectomy and oophorectomy (in patients with mammary carcinoma), has discussed probable sources of estrogen production after bilateral oophorectomy and adrenalectomy. The main purpose of Strong's investigation was to seek evidences of residual adrenal cortical tissue after bilateral adrenalectomy.

One possible explanation for a lack of response to adrenalectomy is the persistence of fragments or rests of aberrant adrenal cortical tissue, and Strong notes that Graham[2] reported histologic evidence of adrenal cortical tissue in the region of the celiac artery in 32 of 100 necropsies. Since Strong's patients did not show evidence of increased cortical function after the administration of ACTH, however, he concluded that in all such instances the operation (adrenalectomy) must have been complete, and that the amounts of estrogen present in the urine of the patients after oophorectomy and adrenalectomy did not, therefore, come from residues of adrenal cortical tissue.

Gompel,[3] of the University of Brussels, Belgium, has recently reported a study of vaginal cytology after oophorectomy and adrenalectomy. Gompel emphasized that Struthers' observation, as well as those of Strong and coworkers, was misleading in suggesting that significant quantities of estrogen continue to be produced after bilateral oophorectomy and adrenalectomy. Gompel observed that no such persistence of estrogen production was suggested in a single one of the 27 cases followed in his study, and concludes that Struthers, and Strong and associates did not follow their patients long enough to observe the complete disappearance of estrogen production. Gompel believes that, when estrogen production stops, the body tends either to store estrogens for a surprisingly long time, or temporarily employs a source of synthesis which does not persist. In every one of his cases, the vaginal cytology eventually revealed an atrophic smear, though Gompel observed several patients whose smears continued to show some estrogenic effect for as long as 9 months after both ovaries and both adrenals had been removed.

At the present time the potentialities of the extraovarian sources of estrogens in any one individual are not predictable. It is therefore evident we should recognize that the removal of any woman's ovaries may be followed by cessation of her ability to produce estrogens. The literature now includes considerable evidence that removal of an individual's ability to produce estrogens during her preclimacteric and her earlier postmenopausal years may result in certain disabilities and in some individuals even death at an earlier-than-average age.

Until the report of Griffith,[4] few gynecologists or surgeons were aware of the evidence that had been accumulating to suggest that ovarian hormones and particularly the estrogens seem, in many women, to confer an immunity

to the development of arteriosclerotic disease. The reports of Wuest,[12] Griffith,[4] Rivin,[7] Corprin,[1] Underdahl,[11] and their co-workers warrant a careful appraisal by any operator tempted to remove apparently normal ovaries. Wuest, in particular, has emphasized that decade by decade the incidence of severe atherosclerosis will be found to be from 10 to 45 per cent higher in women oophorectomized before the age of 50 when they are compared with women of equal age whose ovaries had not been removed.

The importance of the postmenopausal production and utilization of estrogenic hormone has been suggested by the severity and yet the reversibility of some of the vascular, bony, and epithelial changes which develop in some women whose ovaries had been removed before the average age of the climacteric. A lack of estrogen in younger women is associated with a higher-than-average incidence of hypertension and atherosclerosis. A proportion of older women develop osteoporosis or discomforts and dysfunctions incident to atrophic epithelial changes associated with a lack of estrogens.

Not more than 60 per cent of women over 60 years of age show cytologic evidences of estrogenic deficiency, and only 20 per cent of such older women shows a clinically evident degree of atrophic vaginitis. It is interesting to note that the atrophic changes of epithelial membrane do not appear to be very generally recognized as problems of any importance. The otolaryngologist occasionally notices atrophic rhinitis, but he does not seem to consider the castrate as a specific problem. In like manner, many urologists feel that some of the dysuria reported by older women may be relieved by the ingestion of sufficient estrogenic hormone to relieve them of the clinically evident degree of atrophic vaginitis so frequently observed in such patients. The advantages of small amounts of estrogenic hormone in facial creams as publicized by the manufacturers of cosmetics must be apparent to us all.

The frequency of discomfort and disability due to osteoporosis is not generally known. So-called senile osteoporosis and the "postmenopausal type" now seem to be regarded as essentially one and the same type of deficiency. A lack of estrogens and androgens seems to be an important factor in the development of such bone changes. The relationship of these lesions to a deficiency of estrogenic and androgenic hormones seems evidenced by the promptness with which patients respond, both clinically and radiographically, to the administration of a combination of testosterone, 10 parts, and estrogens, one part. The role of estrogenic hormone in the production of this lesion seems evident, moreover, when we consider that in most reported series women outnumber men 3 or 4 cases to one.

Rivin and Dimitroff[7] reported in 1954 that: (a) males treated with estrogen have less atherosclerosis than ordinary males, and (b) oophorectomized females have an incidence of severe atherosclerosis approaching that of the male.

Griffith[4] thinks that many oophorectomies are being performed simply because the operator believes that woman's ovaries have fulfilled their biologic purpose when childbearing is no longer possible. He believes that so-called prophylactic removal of ovaries will eventually be recognized as unwise when eventually we have more knowledge concerning the extent to which ovarian hormones enter into the metabolic processes of tissues distant from the genitourinary tract. Surgeons and gynecologists nevertheless continue to recommend removal of the ovaries and continue to perform oophorectomy whenever a hysterectomy is indicated and the woman is approaching the climacteric. The observations reported herein suggest that 20 to 30 per cent more women who have been castrated show an "estrogen deficiency" type of

smear than women whose ovaries were preserved when the uterus was removed. This difference is noticeable whether we are comparing the incidence of atrophic changes 2, 5, 10, or 15 years after cessation of the menstrual cycle.

The psychological aspects of preservation of the ovaries should not require emphasis. We all know that in the minds of all women the loss of ovarian function is associated with old age. There is little evidence that women are biologically better suited to cope with the emotional conflicts of middle age and of older age after removal of the ovaries. Shelton[8] believes that, as women grow older, estrogens help keep them looking, feeling, and acting younger.

Conclusion

In conclusion, certain impressions seem to warrant emphasis at this time. Removal of the ovaries and the withdrawal of estrogens should not be considered one and the same, for the effects are not identical. The so-called extrapelvic sources of estrogen seem able to protect not more than 50 per cent of apparently normal women from the possibility of atherosclerosis and osteoporosis, or from the certain development of atrophic epithelial changes in the genitourinary tract, and it seems timely to ask whether prophylactic oophorectomy is ever justified.

We believe we have observed evidence that the ovary seems to be the source of a significant proportion of the estrogens affecting the tissues of a majority of women for years after the menopause. Unfortunately, the patients we have been able to study have, however, provided little information concerning two important aspects of this problem and we need answers to the following: (a) if both ovaries are removed prophylactically and routinely, *what proportion* of patients so castrated will actually experience the discomforts and disabilities due to atrophic changes, and the possibility of an occasional death due to the development of cardiovascular disease at an earlier-than-average age, and (b) how completely can the undesirable effects of estrogen withdrawal be avoided by long-continued administration of replacement therapy?

It is evident that ovarian hormones circulate throughout the body and, by alterations of metabolic processes distant from the reproductive tract, must affect tissues other than those lining the uterus and vagina. It seems evident that the production of estrogen by the so-called extrapelvic sources is not predictable, and as a result the effects of removal of the ovaries are not predictable. Oophorectomy when the ovary appears normal now seems questionable at any age and is particularly to be avoided in younger women.

The absence of estrogen, particularly during the years before women usually experience spontaneous cessation of periods, may be accompanied by the development of such changes as atrophic vaginitis, osteoporosis, and atherosclerosis. Such changes may result in discomforts and disabilities and may eventually shorten the lives of some individuals so affected.

Since, in our experience, castration results in an evident deficiency of estrogenic effect in 40 per cent of women within 5 years and in over 50 per cent of women after 10 years, it seems likely that oophorectomy, if performed

routinely whenever hysterectomy is indicated, could contribute to the eventual disability of more women than now seem destined to develop a malignancy of the ovary.

References

1. Corprin, A. C., Lewis, L. A., Dustin, H. P., and Page, I. H.: Ann. New York Acad. Med. **64**: 620, 1956.
2. Graham, L. S.: Cancer **6**: 149, 1953.
3. Gompel, C.: Unpublished paper presented at First Pan American Cancer Cytology Congress, Miami, Florida, April 26, 1957.
4. Griffith, G. C.: Obst. & Gynec. **7**: 479, 1956.
5. Livingston, G. B.: J. Obst. & Gynaec. Brit. Emp. **61**: 628, 1954.
6. Master, A. M., Marks, A. B., and Dack, S.: J. A. M. A. **121**: 1251, 1943.
7. Rivin, W., and Dimitroff, S. P.: Circulation **9**: 533, 1954.
8. Shelton, E. K.: J. Am. Geriatrics Soc. **2**: 627, 1954.
9. Strong, J. A., Brown, J. B., Bruce, J., Douglas, M., Klopper, A. I., and Lorraine, J. A.: Lancet **2**: 955, 1956.
10. Struthers, R. A.: Brit. M. J. **1**: 1331, 1956.
11. Underdahl, L. C., and Schmit, H. H.: Proc. Staff Meet., Mayo Clin. **72**: 749, 1947.
12. Wuest, J. H., Dry, T. J., and Edwards, J. E.: Circulation **7**: 801, 1953.

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Discussion

DR. FRANK R. LOCK, Winston-Salem, N. C.: The reception of studies which are apt to have a general influence on gynecologic practice is usually determined by individual prejudices. A controversy has existed concerning the wisdom of oophorectomy since Battey's recommendation of castration in the treatment of neurasthenia and insanity in 1865. A few adherents to Battey's concepts seem to continue in surgical practice.

In the present study Dr. Randall has confirmed the observations of previous investigators concerning the persistence of estrogen activity after physiologic and artificial menopause as appraised by cytologic techniques. This method is accepted for evidence of estrogen effect and there is some reported correlation between cytologic changes and estrogen level as determined by biologic assay. However, I wish to ask Dr. Randall how much the cytologic characteristics are influenced by sexual activity, chemical agents used in the vagina, and infection or other gynecologic pathology. The smears in the present study were taken by the Ayers spatula technique of cervical scraping. Does this method provide a satisfactory correlation when compared with cells obtained from various levels in the vaginal epithelium?

Dr. Randall's observation of estrogen deficiency and estrogen effect in castrates correlates with the observations of Struthers and others. Dr. Randall finds an increased incidence of estrogen deficiency in castrates as compared to that observed by others.

He believes there is a decreased incidence of hypertension in patients who show persistent estrogenic effects, although no particular increase in the incidence of hypertension was observed in those with estrogen deficiency.

Dr. Randall is attempting to stimulate the interest of gynecologists in preservation of the ovary on the basis of the recent concept of the relation of atherosclerosis, osteoporosis, and other metabolic changes to estrogen lack. He has given little consideration to the psychological and emotional effects of castration.

The evidence in favor of increased atherosclerosis in the absence of estrogens is based on the lower incidence of the lesion in women as compared to men, and upon experimental evidence in rabbits and fowl. The effect of estrogen therapy on serum lipid patterns in these experimental animals is marked. It is recognized that rabbits have a marked predilection to atherosclerosis. In the cockerel the egg-laying cycle extensively affects serum lipids, and experimental data in this animal are difficult to interpret from the point of view of man. The experimental use of endocrines in the human in physiologic doses has produced equivocal results, and massive doses result in relatively slight changes

in the serum lipid patterns. However, the short time of experimental observation in the human may not truly indicate the effect of estrogens in degenerative vascular disease.

Donaldson and Nassem, Albright, and others have investigated extensively the relationship of castration to osteoporosis and have observed no consistent results.

It may be significant that Donaldson found a decrease in libido in 65 per cent of his group of patients subjected to artificial menopause.

Valid argument for removal of the ovaries at the time of hysterectomy is the possibility of subsequent development of carcinoma of the ovary or benign ovarian lesions requiring a secondary operation. Emphasis was given to this danger by Counseller's observation of 65 cases of cancer of the ovary subsequent to hysterectomy. Since the number of hysterectomies related to this series of cases was not known, no incidence of carcinoma of the ovary following hysterectomy was suggested.

I certainly agree with Dr. Randall that the risk of preserving any ovary is no greater than the incidence of ovarian malignancy, namely, 9 cases per 1,000 women.

Griffith and others are convincing in their arguments and are fostering the concept that the ovaries are not concerned primarily with the sexual and reproductive life but play a significant metabolic role, particularly in anabolic or nitrogen-retaining effects. There is an increasing tendency to recommend routine and continuous administration of estrogens when castration is required or elected in surgical treatment. Some would question whether the carcinogenic risk of continuous estrogen administration is greater than the danger of spontaneous carcinoma of the ovary.

It is unfortunate that the present evidence of the influence of castration on the incidence of atherosclerosis, osteoporosis, and metabolic imbalance is inconclusive. The danger of carcinoma of the ovary is certainly not great enough to warrant an arbitrary position concerning castration at a given age. A consistent attitude by gynecologic specialists would follow clarification of this problem.

Robert Battey appeared before this Society in 1877 to present a paper entitled, "Is There a Proper Field for Battey's Operation?" A quotation is pertinent to our discussion of the pros and cons of removal of the ovaries: "I appear before you today, not as the advocate of a special operation, but as an earnest searcher after truth and wisdom, hoping to find the more excellent way by which we are to lead the deplorable invalids, whose agonizing sufferings of mind and body have so often touched my tenderest sympathies, out of the darkness and gloom of despair into the light of life and health."

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I wish to contribute purely for the record an evaluation of the estrogenic effect observed in women beyond the age of 45 as obtained by vaginal smears. The figures were obtained from a routine screening project carried out several years ago under the auspices of the Philadelphia Division of the American Cancer Society. The data presented were prepared for me by Dr. A. E. Rakoff, Director of the Cytology Laboratory in the Department of Obstetrics and Gynecology at Jefferson Medical College Hospital.

The series includes 909 women without demonstrable pelvic lesions or illness who were selectively placed in three age groups:

420 from 45 to 50 years
388 from 50 to 60 years
101 from 60 to 70 years

The comparative criteria for each of the three age groups were as follows: (A) Estrogen *deficiency*—marked, moderate, or slight, and B) estrogen *effect*—marked, moderate, or slight. The findings shown in the table were noted:

AGE	NO FRANK ESTROGENIC DEFICIENCY (%)	ESTROGEN EFFECT		
		SLIGHT (%)	MODERATE (%)	MARKED (%)
45 to 50 years	61	33	16	12
50 to 60 years	29	17	9	3
60 to 70 years	15	8	5	2

These figures should present a reasonably satisfying base line for comparison with those presented by Dr. Randall and his associates, by indicating what the expected findings might be had no surgical intervention occurred. Supporting data relative to technique, etc., are omitted as not specifically pertinent to the purpose of these remarks.

DR. RONALD R. GREENE, Chicago, Ill.—We also have been interested in how much estrogen is produced in the normal postmenopausal female, using material which is less sensitive in the vaginal mucosa but which is not subject to the influence of intercourse or douches or other trauma. The uteri which had been removed for plastic purposes from 335 women were studied for evidences of estrogenic stimulation in the endometrium. All women selected for this study had to be at least 2 years postmenopausal and had received no hormone therapy and had had no bleeding. Our findings are not in good agreement with those reported by Dr. Randall. Using the endometrium only, we found estrogenic stimulation in only 4 of the 335 women; 3 had hyperplasia and 1 had proliferation. I repeat that these were *normal* postmenopausal women only.

DR. C. LEE BUXTON, New Haven, Conn.—Possibly there are a couple of areas of confusion in our thinking concerning measurement of ovarian activity and also the difference between what might be called an artificial menopause and a natural one. I wonder whether measurement of estrogen activity is a real measurement of ovarian function. Dr. Randall mentioned, and we all know, the possibility of production of estrogen from other sources. It seems to me it might be possible that when an individual is deprived of her greatest and most normal source of estrogen production, other glands, such as the adrenal, may take on this responsibility so that a number of these women may acquire their estrogen from other sources and in fairly satisfactory amounts.

Another aspect of this situation is important and that is the difference between castration at an early age due to radiation or removal of the ovaries and the presumably normal cessation of function that occurs at the time of the menopause. If we try to group these two types of ovarian abnormalities together we may be making a mistake. If we assume that the menopause is a physiologic function for the human female, presumably she is capable, following a natural menopause, of taking care of her own estrogen deficiency without production of protein imbalance or osteoporosis, whereas in a younger woman who has a much greater physiologic need of estrogen there might develop the more serious aspects of estrogen deficiency.

DR. RALPH A. REIS, Chicago, Ill.—May I ask two questions: (1) Dr. Randall, do you consider surgical castration the same as irradiation castration where ovarian stroma is still present and so frequently functions? (2) Do you have any way of knowing how many of this large group have had any estrogen therapy in the intervening years betwen the menopause and the time they were evaluated by smear?

I do not believe this question of whether the ovaries should be taken out or left in is going to be settled today. We will be influenced by our own experience.

DR. RANDALL (Closing).—I apologize for the fact that I am not going to answer one significant question: How much are these smears influenced by factors other than the amount of estrogen the patient might have in her circulation? To answer would involve considerable discussion and show little consideration of our time schedule.

I can, however, assure Dr. Reis that, when there was any reason to believe that a woman had been receiving estrogens, we very carefully omitted her from the study. These patients have been observed in our office over a considerable period of time and for the most part represent estimations of estrogen effect in the smears of women who come in for routine pelvic examination. The majority have been examined repeatedly over a period of time, and I believe we know the ones who have been receiving estrogens.

I can certainly agree with what I believe Dr. Buxton was emphasizing: that the only point of all this is that some women do not have extraovarian resources to produce the estrogens they need in order to be protected from some of the undesirable effects that

some castrates develop. Since we have no way of knowing which woman has extra-ovarian sources of estrogen that are adequate for her needs, we are cautious about castration. Unfortunately for the purpose of this report, we do not have many castrates to study.

Dr. Reis, I agree that castration by surgery and by irradiation may not result in the same situation. I believe it was learned in the management of prostatic carcinoma that the giving of stilbestrol and castration by irradiation do not always accomplish the same thing as orchiectomy.

This report is largely a plea to you who believe in prophylactic removal of the ovaries to bring forth more convincing evidence than I have seen to date in support of the contention that castration does no harm. I particularly agree with Dr. Lock that it is difficult to ignore evidence that estrogen protects women from arteriosclerosis.

Some of the implications are grim.

When we consider the number of ovaries that have been removed in our efforts to protect women from the risk of ovarian cancer, as more and more women take up the knife in our hospitals, it seems inevitable that they will soon be convinced that they should castrate us males to save us from arteriosclerosis.

Then we will know, no doubt—though we may not actually live longer—that to the castrate life at least seems longer.

SEX STEROID INFLUENCE ON THE AGING PROCESS*

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THE aging phase of the human life span has as many different facets as do the preceding stages of growth and mature function. There is, however, one unique aspect of the aging process that is difficult to demonstrate in either of the other two main divisions of human existence. Many physiological involutionary processes are either partially or completely reversible, subsequent to properly controlled, stimulative therapy.

The only known member of the female gender to live past her period of reproductivity is the human female.[1-4] The postmenopausal years represent, for her, a socially conditioned phenomenon. Historically, there is no evidence that the age at onset of the climacteric has varied with succeeding generations of women.[5] It follows, then, that postmenopausal life has emerged as a consequence of the great increases in life expectancy developed over the last hundred years. Since the efforts of the medical profession have been directly responsible for providing the final two decades of the female's life expectancy, the profession must accept the responsibility of developing effective physiological support during the ever-lengthening involutionary phase of human existence.

Most physiological episodes of growth and mature function are either initiated or controlled by the glands of internal secretion. Consequently, the apparent inability of one of the elements of the endocrine system to maintain clinically effective secretory function during the involutionary years becomes a point of significant investigative concern. It is important that the secretory activity of the entire endocrine system during the involutionary years be thoroughly appreciated, if we are ultimately to evaluate the role of the sex steroids in the aging process.

The experimental measure of pituitary function during the postmenopausal era has been primarily confined to laboratory observations of adrenocorticotrophic hormone production, and gonadotrophin evaluation. Observations in the field of adrenal stimulation have established the continued interglandular stimulative effects of both pituitary and adrenal glands during the aging process.[6,7] As the result of this mutually stimulating axis, little or no reduction has been described in clinically effective adrenal corticoid hormone production during the aging process.

The laboratory definition of urinary gonadotrophin levels presents a somewhat different picture. Albert[8] has published data to support the evaluation of gonadotrophin production in the aged described by our own laboratory.[9]

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A peak concentration of urinary gonadotrophin production apparently develops somewhere between the ages of 50 and 70 years. This immediate postmenopausal rise in urinary gonadotrophin excretion is not maintained throughout involutionary life. During the eighth and ninth decades, there is a significant drop in gonadotrophin secretory activity to new base line levels, which are approximately half those of the immediate postmenopausal era. Of real significance, however, is the interesting observation that even in the 80 year age group, there is still definitive, measurable gonadotrophin production despite the admitted inadequacies of our present crude laboratory bioassay techniques.

For years, investigative attention has been directed toward the function potential of the thyroid gland during the aging process.[10] The first definitive work noted that the decreased rate of oxygen consumption in individuals above the age of 77 was only 12 per cent below the average of men between the ages of 20 and 50.[11] Recent studies of serum protein-bound iodine levels in the aged indicate that the spread of blood iodine levels is about the same for the aged individual as those of younger adults.[12] There is further evidence along this line in recent animal experimentation[13] which concludes that the reduction in thyroid secretion of older animals is a homeostatic adjustment to diminished requirements of target tissue rather than inadequacy of glandular secretory potential.

These first efforts to evaluate thyroid function in the aged population need more definitive experimental support before any absolute conclusions can be drawn in relation to the effectiveness of thyroid secretory activity during the involutionary years.[14] It is certainly true, however, that there is no evidence to date of lack of effective thyroid secretory function, even within the 80 year age group.

The activity of the adrenal gland, during the "neutral gender"[15] phase of life, is at once an excellent example of semi-independent secretory productivity, and a cause for concern because of the resulting imbalanced protein and calcium economy. The effects of unopposed adrenal secretory activity will be discussed when ovarian dysfunction is considered. Suffice it to say, multiple investigators[16-18] have confirmed the potential of adrenal activity during the aging process. There is every evidence that the adrenal, alone of the endocrine chain, continues mature secretory function essentially independent of the aging process, and without significant interglandular stimulation. This is probably true despite the continued existence of a pituitary-adrenal axis.

For years the pancreas has been known to retain its function potential, even in the 80 year age group.[19] While there is an estimated reduction of secretory activity of from 15 to 20 per cent (when compared to the 30 to 40 year age groups), there is every indication that this reduction in secretory activity is more than counterbalanced by the functional reserve of the pancreas. Present evidence certainly suggests that, except in established diabetic states, the pancreas is not rendered incapable of adequate physiological supportive function by the aging process. It is true, however, that many potentially diabetic individuals, who have surived even the exigencies of childbearing without demonstrating the stigmas of the disease, do become actively diabetic during the postmenopausal years. At present, the exact means by which protection is afforded a potential diabetic by adequately maintained sex steroid levels has not been defined.

Ovarian function during the postmenopausal years needs more definitive interpretation. Although the menopause does represent a major involutional phase in ovarian function, it certainly does not indicate an end point of steroid production.[20-22] Ovarian productivity during the aging process has extreme

individual variation. This is the basic reason for the 15 year age spread[23] (from the early forties to the mid-fifties) in the onset of the symptoms of the climacteric.

The dual physiological role of the ovary must be re-examined in view of the contention that the postmenopausal years represent a socially conditioned phenomenon. We fequently fail to define the relative importance of the two spheres of ovarian influence. Certainly, the primary function is that of reproduction. Infinitely more important to the physical and mental well-being of the individual woman is the secondary role of the ovary—that of catalyst (through its sex steroid production) to many different phases of basic physiological activity. If only reproductive activity failed during the postmenopausal years, and sex steroid production were adequately maintained, there would be no definition of a "neutral gender." Unfortunately, as reproductive activity fails, so does clinically effective sex steroid production retrogress. The involution rate of clinically effective steroid production does lag, when compared to the rapid retrogression of reproductive function, but this lag is seldom seen to last more than a decade.

It is obvious that the pituitary-gonadal axis, so evident as a mutually stimulative mechanism during mature life, fails as the aging process progresses. The residual ability of the pituitary to secrete the gonadotrophic elements during the postmenopausal years has been completely established.[8, 9] Thus, it is evident that the ovary loses its responsiveness to previously established normally stimulative channels. Unfortunately, no other source of effective gonad stimulation develops during the aging process. The postmenopausal inability of the gonadal elements to respond effectively to pituitary stimulation is the "Achilles heel" of the entire endocrine system.[24] With clinical failure of the gonad, the fine balance of mutually stimulative secretory function, or interglandular dependence, is lost to the entire endocrine chain.

From a humoral point of view, the basic picture of the aging process becomes one of independent secretory activity by the individual elements of the endocrine chain. With the exception of the pituitary-adrenal axis, the aging process slowly destroys the essence of interglandular stimulation during the decade subsequent to the actual menopause. Each member of the endocrine chain, with the exception of the gonad, is perfectly capable not only of independent function, but of returning to its peak levels of secretory efficiency, even during the seventh and eighth decades of life, if a proper glandular balance pattern of mutual stimulation is re-created.

To re-create the proper balance pattern of endocrine secretory activity, the clinically inadequate levels of postmenopausal ovarian steroid production must be supplemented. Again, it should be emphasized that there is no question that ovarian steroid production does continue, even into the 60 year age groups.[20-22] This level of secretory activity, however, is usually inadequate to protect the aging female against such significant metabolic distresses as protein imbalance and exhaustion of calcium storage.

If substitution therapy with the sex steroids is to be considered, as a matter of positive protection, their basic contribution to protein balance should be thoroughly appreciated. We must also consider, as a form of negative protection, the opposition provided by the sex steroids to the catabolic effects of the corticoid hormones. The anabolic influence of such compounds as testosterone, estradiol, and their derivatives has been defined in the past by clinical observation. These observations have recently been reinforced by detailed laboratory evaluation.

For clinical observation of sex steroid anabolic action, we must turn to early childhood for the first well-documented cases of sexual precocity, both male and

female. There is not only marked development of primary and secondary sexual anatomy, but also exceptional growth of height, weight, musculature, and skeletal development.[25-28] Observations of the course of physical events subsequent to the development of steroid-secreting tumors of the ovaries (granulosa-cell tumors) and of the testes (Leydig-cell tumors) have also rewarded attempts to evaluate steroid influence on protein metabolism. Granulosa-cell tumors in children not only promote rapid growth of sexual anatomy, but, frequently, an acceleration of skeletal growth, and occasionally excessive somatic development.[28, 29] In mature males, a characteristic retention of strength, muscle mass, and energy until the terminal stages of Leydig-cell carcinomatosis has also been well documented.[30]

Finally, clinical observations of results of gonad stimulation from external sources such as pituitary gonadotrophin or chorionic gonadotrophin,[31, 32] and of direct steroid replacement in eunuchoid males and females with ovarian agenesis have been rewarding. The effect of pituitary gonadotrophin on the Leydig cells of males with hypogonadism (with subsequent production of androgenic hormone) has been observed to produce growth of marked primary and secondary sexual characteristics. There also has been exacerbation of the growth rate of the skeleton and muscle mass of individuals under therapy. The estrogenic hormones have also been stimulated in females with hypogonadism by chorionic gonadotrophin. Although a significant stimulative effect on the growth of protein and osseous tissues has developed, it is certainly of a lesser degree than that noted for the males with hypogonadism.

Finally, as a means of laboratory evaluation, the direct replacement of estrogenic substances and testosterone in eunuchoid males and females with ovarian agenesis has been followed with metabolic balance studies in addition to the usual clinical observation and measurement techniques.[33, 34] Both males and females have shown retention of nitrogen, phosphorus, potassium, and sulfur in proportions roughly similar to the presence of these basic elements in protein tissue.[35, 36] Significant increase in skeletal development and muscle mass has been simultaneously recorded in these individuals under the influence of direct replacement therapy.[36, 37]

Since sex steroid influence on protein tissue metabolism has been well established, the marked change in skeletal growth at puberty and successful reclamation of clinically distressing osteoporosis are better understood. Fundamentally, the mechanism by which these phenomena are produced is by progressive deposition of bony matrix (a protein material). In steroid starvation states (for young and old alike) there is prompt wastage of the matrix material, particularly from the long bones of the body. Without a sufficient amount of this web-like matrix material, calcium concentrations are markedly lowered. In truth, a reversal of the usual deposition process occurs, and states of osteoporosis develop. Once the bony matrix is returned to effective levels by any protein anabolic mechanism, calcium deposition is promptly effective and osteoporosis successfully combated. A preliminary report[38] on bone formation in different age groups describes the actual rates of bone formation in cases of osteoporosis as essentially the same as those of normal adults of similar age groups. Thus, when the bony matrix is redeposited under the anabolic influence of the sex steroids, calcium deposition is resumed at its usual unabated rate. By this mechanism, clinical osteoporosis immediately becomes a reversible process. In essence then, there is no such thing as old bone, if satisfactory sex steroid balance and adequate protein intakes are maintained during the aging process.

In an excellent review of this subject, Reifenstein[39] points out that studies on varying types of osteoporosis indicate that there are quantitative differences between the effects of testosterone and estradiol compounds on the anabolism of

protein and osseous tissue. On protein tissue, male sex steroids have a greater anabolic effect than female sex steroids. The combination of both steroids (given as a unit) has no significantly greater effect on pure protein deposition than that of testosterone substances alone.[40] On osseous tissue, in contrast, estradiol agents have a greater anabolic effect than the testosterone components.[41] Interestingly enough, the combination of both steroids has a more marked effect on osteoporosis than either of the substances used individually.[42, 43] The reason for this variation in effective anabolic influence by the sex steroids, used either individually or in combinations, is completely unknown to date.

We must also consider in passing the catabolic effects of the corticosteroid hormones upon protein tissue. As previously described, the corticosteroid production of the adrenal cortex appears to be relatively unaffected by advancing age.[6] Members of the "neutral gender" gradually develop a relative excess of endogenous catabolic corticoid hormones in direct proportion to the decrease of the endogenous anabolic sex steroid production. The hormone imbalance thus becomes qualitatively that of the Cushing syndrome. This relative excess of the catabolic steroids may also be an important factor in the development of the protein depletion described in osteoporosis.

It is also obvious that any factor which would cause an imbalance in normal protein or osseous tissue metabolism, such as prolonged malnutrition, or any chronic debilitating disease, would tend to enhance the catabolic effect of the corticoid hormones during the aging process. Despite this influence of the corticoid steroids toward protein depletion, evidence at present seems to support the contention that the sex steroids are fundamentally anabolic in their function, rather than anticatabolic. However, the possibility of a generalized anticatabolic action by the sex steroids cannot be denied.

While the influence of sex steroids on protein metabolism is of primary importance during postmenopausal life, the protean influence of these steroids has also been demonstrated in many other aspects of our physiological body economy. A good example of this diversified influence is the recently reported effect of ovarian hormones on cardiovascular tissue.[21] The demonstration of an advanced degree of coronary atherosclerosis determined in bilaterally oophorectomized women[20] as opposed to normal controls has opened a completely new field for the investigative consideration of the research cardiologists.

A detailed evaluation of involutional senile mental aberrations, as well as the possibility of their control under long-range sex steroid support,[44] has stimulated yet another field of investigative interest. Such basic mental processes as memory for recent events, powers of definitive thinking, the ability to absorb new material have all shown significant improvement when a steroid-supported aged population was evaluated in a series of controlled experiments. These patients were evaluated independently by members of the Washington University Department of Neuropsychiatry,[45] while under supervised steroid replacement by our own Department. The patient evaluation was carried out under the strictest possible clinical control. Measurable improvement under replacement therapy usually reaches an end point in attainment of reclamation within a year after the initiation of steroid supportive measures.

Once a plateau has been reached in such reversible psychological involutional symptoms as the reclamation of definitive thinking, further improvement is essentially negligible. The reclamation plateau attained varies with each individual, usually in direct relationship to the beginning of therapy. The earlier in the complex process of senile mental involution that sex steroid support is initiated, the better the ultimate result. There is obviously a level of senile mental involution beyond which there is no recall under sex steroid influence. Unfortunately, this level is attained quite early in the involutionary process of mental

aging. It should also be mentioned that continued steroid support does not prevent some instances of a slow reversal to mental senility of satisfactorily reclaimed patients. This mental involutionary process is certainly slowed over a period of years, however, when compared to the rapid disintegration rate of unsupported patients.

Sex steroid influence on the target organs during postmenopausal life has been defined in detail during the past decade. With the exception of the ovaries, the pelvic organs and the breasts are perfectly capable of reversing their senile involutional status, and of returning to apparently normal size and function under the influence of exogenous steroids. This characteristic of the target organs has provided an unusually effective means for clinical and laboratory humoral investigation.

During the past twelve years, the senile pelvis has provided the opportunity for detailed evaluation of estrogen, progesterone, and testosterone influence, both individually and in combined dosages. Estrogen bioassay experiments[46] on the intact corpus have been of invaluable aid in determining length of influence and comparable milligram potency of multiple different estrogenic compounds. Withdrawal bleeding times, endometrial biopsies, and vaginal smears have provided additional information as to function.

The estrogen-stimulated uterus in turn has provided a base line opportunity for both progesterone and testosterone determination. Detailed investigation of the influence of progesterone dosage has been made possible, with attention paid to such diverse interests as the dosage in milligrams necessary to effect withdrawal bleeding, and progesterone breakthrough phenomena.[47] A definition of the comparative values of aqueous crystalline versus oil-suspension progesterone[48] has produced additional functional information in the field of endometrial physiology. Finally, the clinical syndrome of irregular shedding of the endometrium has been reproduced experimentally[49] for the first time in the senile uterus stimulated under controlled endocrine therapy.

The influence of testosterone on the estrogen-primed endometrium has also been exhaustively investigated.[50, 51] The luteal effects of testosterone on the estrogen-stimulated human endometrium have been described as the result of investigations of the target organs. This luteal effect of testosterone on the endometrial stroma and glands is roughly one-tenth as potent as that of progesterone in an absorbed milligram-for-milligram comparison ratio.[52] Finally, the presently conceived 20-1 testosterone-estrogen combination has been derived from multiple replacement experiments with varied adjustments of dosage.[53, 54]

It is evident that Schorr's[55] original theoretical concept of combining the two sex steroids for mutual synergistic action has been brought to clinical fruition by the use of the senile uterus as an experimental proving ground. This clinically effective steroid dosage is but the end result of numerous other experiments with combinations of replacements conducted throughout this country[56, 61] since 1938.

It should also be mentioned that the basic stimulative effects of the sex steroids on the acinous tissue of the breast have been defined and described.[62] These results have been primarily obtained from autopsy opportunities. From a clinical point of view, it is fortunate that the experiments with the long-range supportive type of steroid replacement have also provided ample opportunity for a basic evaluation of sex steroid influences on the target organs.

If the postmenopausal woman is to be subjected to sex steroid influence in excess of her own minimally produced complement, every precaution must be taken to protect her from the unpleasant results of uncontrolled therapy. The untoward results of breast and pelvic organ stimulation which cause concern are

uterine bleeding, hirsutism, or excessive breast growth. The possible carcinogenic effects of the sex steroids on these target organs must also be considered. This remains an anathema to many physicians.

There are four possible techniques for steroid replacement in an aging woman without accompanying concern for such pathological developments as endometrial hyperplasia and resultant breakthrough vaginal bleeding. As a first alternative among these techniques, estrogenic compounds may be offered in a cyclic manner. The estrogenic influence may be withdrawn for one week in approximately every four to allow the endometrium to slough, and avoid the possible development of hyperplasia. As a second method, estrogen influence may be maintained indefinitely, and the uterine endometrium cyclically and regularly sloughed with exhibition of an adequate progesterone counterbalance. As a third technique, estrogen influence may be maintained and the uterine endometrium may be regularly sloughed by cyclic testosterone exhibition in a manner similar to that described for the use of progesterone. Finally, there remains the clinically preferable technique of avoiding any significant growth of uterine endometrium which might result in breakthrough vaginal bleeding. This calls for a combination of estrogenic and androgenic influence administered as a unit form of medication.[63]

The combination of testosterone and estrogen (initially testosterone propionate and estradiol benzoate in a ratio of approximately 20-1 of milligrams absorbed has numerous advantages.[54] Aside from possible vaginal spotting between the fourth and sixth weeks under therapy, the patient should not bleed on this ratio of combined steroids regardless of the length of supportive therapy.

The theoretical possibility of developing carcinoma of the endometrium on the basis of establishing a carcinogenic precursor of transitory endometrial hyperplasia[64-67] is voided by the steroid combination technique. The endometrium is so senile after six months of replacement therapy that it is virtually impossible to obtain sufficient tissue for pathological examination by endometrial biopsy techniques. Endometrial hyperplasia simply does not occur under this type of replacement influence.[53]

The techniques of replacement with combined steroids will also pacify many of the militant objectors to other types of steroid replacement by basically avoiding stimulation of secondary sex characteristics. While there is a passing breast tenderness, lasting from four to six weeks, this tenderness will not return once the initial stimulative phase has been passed. Irritation, engorgement, or even hypertrophy of the clitoris, so prevalent in replacement attempts restricted to testosterone alone, will not be a clinical factor.

Hirsutism and/or lowered vocal pitch in the absorbed 20-1 ratio is a problem in approximately 20 per cent of cases. It is possible that corticoid secretion from postmenopausal activity of the adrenal may well be the deciding factor in producing facial hair. If hirsutism appears while the patient is under treatment, the ratio should be dropped to approximately 15-1 of milligrams absorbed, testosterone over estrogen. Lowered vocal pitch is a more presistent distress and one which has resisted alleviation in susceptible individuals.

The gerontotherapist, using the presently considered 20-1 steroid replacement technique, will be confronted by many problems. Each patient needs a significant degree of individual evaluation and careful observation while under the supportive influence of the sex steroids. What, then, may the future hold for steroid replacement techniques? It is certain that the presently accepted techniques do not by any means represent the end point of steroid replacement therapy.

The future of sex steroid replacement rests with our ultimate realization that the postmenopausal years represent a socially conditioned phenomenon for every individual. It is obvious that the primary function of the female gonad (reproduction) is at an end with the advent of the menopause. Therefore, attention should be entirely directed toward the gonad's second province (sex steroid production). If it is possible to accept the existence of a "neutral gender" as a medical concept, the roadway through the problems of steroid replacement becomes less tortuous. If the maintenance of the secondary sex characteristics is ultimately regulated to its proper minor consideration, the newer types of steroid replacement now being evaluated clinically may offer possible answers to our concern for adequate replacement techniques.

A steroid-like substance must be developed to include the proved cumulative physical and mental effects of the present combinations, yet contain none of their unfortunate factors of secondary sex stimulation. Once this is accomplished, a major step in overcoming the present inherent disadvantages of steroid replacement will have been taken. Primarily, the anabolic effects of the present steroids on protein and osseous tissues, the possible controlling influence on the progress of atherosclerosis, and the basic regenerative effects on early mental senile involution should be advanced. Also of major moment are the undemonstrated, but indubitably present, positive supportive influences on other basic physiological functions. The factors of secondary sex stimulation which result in such clinical distresses as hirsutism, breast engorgement, and even uterine bleeding, must be removed from the newer supportive compounds. The medication must be long acting, available for oral ingestion, and relatively inexpensive, if we are to have available the proper tools with which to fight the wastage of senile physical and mental involution.

In essence, the present use of sex steroid replacement during the involutional phases of life is an attempt to meet an implied medical responsibility. The socially conditioned phenomenon of postmenopausal life has brought to attention many problems associated with the processes of senile physical and mental involution. These physiological distresses are in many instances partially or completely reversible with the exhibition of judiciously selected combinations of sex steroids. Laboratory and clinical evidence of the catalytic influence of sex steroids in reversing many of the physiological imbalances associated with aging has developed during the last ten years. Present replacement weapons are obviously inadequate to the need. Once the responsibility for the use of supportive techniques is accepted by the medical profession, the development of clinically effective steroid supportive substances is but around the corner. The existence of a "neutral gender" is now a matter of established physiological fact. Our investigative efforts should be directed toward supporting it effectively and attempting to prevent the inherent physiological waste accompanying the aging process.

References

1. Hartman, C. G.: Les hormones sexuelles, Paris, 1938, L. Brouha.
2. Slonaker, J. R.: Am. J. Physiol. 84: 192, 1928.

3. Zuckerman, S.: J. Endocrinol. **5**: 220, 1947.
4. Perry, J. S.: Phil. Trans. B. **237**: 93, 1953.
5. Eckstein, P., and Zuckerman, S.: Memoirs Society Endocrinology No. 4, London, 1955, Cambridge University Press.
6. Pincus, G., editor: Hormones and the Aging Process, New York, 1956, Academic Press Inc., p. 1.
7. Freeman, H., Pincus, G., Elmadjian, F., and Romanoff, L. P.: Geriatrics **10**: 72, 1955.
8. Albert, A., Randall, R. V., Smith, R. A., and Johnson, C. E.: In Pincus, G., editor: Hormones and the Aging Process, New York, 1956, Academic Press Inc., p. 49.
9. Masters, W. H.: In Lansing, Albert I., editor: Cowdry's Problems of Ageing, ed. 3, Baltimore, 1952, Williams & Wilkins Company, p. 651.
10. Aub, J. C., and DuBois, E. F.: Arch. Int. Med. **19**: 823, 1917.
11. Kise, Y., and Ochi, T.: J. Lab. & Clin. Med. **19**: 1073, 1933-1934.
12. Starr, P.: J. Am. Geriatrics Soc. **3**: 217, 1955.
13. Grad and Associates: Meeting of the Gerontological Society, Chicago, November, 1956.
14. Rawson, R. W.: In Pincus G., editor: Hormones and the Aging Process, New York, 1956, Academic Press Inc., p. 34.
15. Masters, W. H.: J. Am. Geriatrics Soc. **3**: 389, 1955.
16. Gallagher, T. F.: Annual Meeting of the American Geriatric Society, San Francisco, June, 1954.
17. Samuels, L. T.: In Pincus, G., editor: Hormones and the Aging Process, New York, 1956, Academic Press Inc., p. 21.
18. Tyler, F. H., Eik-Nes, K., Sandberg, A. A., Florentin, A. A., and Samuels, L. T.: J. Am. Geriatrics Soc. **3**: 79, 1955.
19. Meyer, J., and Necheles, H.: J. A. M. A. **115**: 2050, 1940.
20. Griffith, C. G.: Obst. & Gynec. **7**: 479, 1956.
21. Wuest, J. H., Dry, T. J., and Edwards, J. E.: Circulation **7**: 801, 1953.
22. Randall, C. L.: Am. J. Obst. & Gnec. **73**: 931, 1957.
23. Severinghaus, E. L.: The Management of the Climacteric, Springfield, Ill., 1948, Charles C Thomas, Publisher.
24. Masters, W. H.: Geriatrics **10**: 1, 1955.
25. Rowlands, R. P., Nicholson, G. W., and Weber, F. P.: Guys' Hosp. Rep. **79**: 401, 1929.
26. Stewart, C. A., Bell, E. T., and Roehlke, A. B.: Am. J. Cancer **26**: 144, 1936.
27. Huffman, L. F.: J. Urol. **45**: 692, 1941.
28. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., 1950, Charles C Thomas, Publisher.
29. Talbot, N. E., Sobel, E. H., McArthur, J. W., and Crawford, J. D.: Functional Endocrinology from Birth through Adolescence, Cambridge, 1952, Harvard University Press.
30. Masson, P.: Rev. Canad. de biol. **2**: 169, 1943.
31. Lurie, L. A., and Hertzman, J.: J. Clin. Endocrinol. **1**: 717, 1941.
32. Dorff, G. B., and Hudson, I. M.: J. Clin. Endocrinol. **11**: 343, 1951.
33. Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F. C.: Endocrinology **23**: 135, 1938.
34. Knowlton, K., Kenyon, A. T., Sandiford, J., Lotwin, G., and Fricker, R.: J. Clin. Endocrinol. **2**: 671, 1942.
35. Kenyon, A. T.: Biological Symposia Vol. IX: Sex Hormones, Lancaster, Pa., 1942, The Jacques Cattell Press, p. 11.
36. Kochakian, C. D.: In Harris, R. S., and Thimann, K. V., editors: Vitamins and Hormones, New York, 1946, Academic Press Inc., vol. IV, p. 255.
37. Thompson, W. O., Thompson, P. K., and Taylor, S. G.: Tr. A. Am. Physicians **56**: 75, 1941.
38. Whedon, G. D.: Personal communication, March, 1957.
39. Reifenstein, E. C.: South. M. J. **49**: 933, 1956.
40. Reifenstein, E. C., Albright, F., and Wells, S. L.: J. Clin. Endocrinol. **6**: 232, 1946.
41. Reifenstein, E. C., and Albright, F.: J. Clin. Invest. **26**: 24, 1947.
42. Albright, F.: In Pincus, G., editor: Recent Progress in Hormone Research, New York 1947, Academic Press, Inc., vol. 1, p. 293.
43. Albright, F.: Ann. Int. Med. **27**: 861, 1947.
44. Caldwell, B. M.: J. Gerontol. **7**: 228, 1952.
45. Caldwell, B. M.: J. Gerontol. **9**: 168, 1954.
46. Masters, W. H., and Magallon, D. T.: Proc. Soc. Exper. Biol. & Med. **73**: 672, 1950.
47. Magallon, D. T., and Masters, W. H.: J. Clin. Endocrinol. **10**: 511, 1950.
48. Masters, W. H., Grody, M. H., and Magallon, D. T.: J. Clin. Endocrinol. **12**: 1445, 1952.
49. Masters, W. H., and Magallon, D. T.: Am. J. Obst. & Gynec. **59**: 970, 1950.
50. Klein, M.: Comp. rend. Soc. biol. **127**: 915, 1938.
51. Engle, E. T., and Smith, P. E.: Endocrinology **25**: 1, 1939.

52. Masters, W. H., and Magallon, D. T.: J. Clin. Endocrinol. **10**: 348, 1950.
53. Grody, M. H., Lampe, E. H., and Masters, W. H.: Obst. & Gynec. **2**: 36, 1953.
54. Masters, W. H., and Grody, M. H.: Obst. & Gynec. **2**: 139, 1953.
55. Schorr, E., Papanicolaou, G. N., and Stimmel, B. F.: Proc. Soc. Exper. Biol. & Med. **38**: 759, 1938.
56. Reifenstein, E. C., Albright, F., Parson, W., and Bloomberg, E.: Endocrinology **30**: 1024, 1942.
57. Kurzrok, L., and Rothbart, H.: Am. J. Surg. **56**: 636, 1942.
58. Carter, A. C., Cohen, E. J., and Schorr, E.: In Harris, R. S., and Thimann, K. V., editors: Vitamins and Hormones, New York, 1948, Academic Press, Inc., vol. 5, p. 317.
59. Glass, S. J.: Ann. West. Med. & Surg. **3**: 186, 1949.
60. Glass, S. J.: J. Clin. Endocrinol. **10**: 1616, 1950.
61. Greenblatt, R. B., Barfield, W. E., Garner, J. F., Calk, G. L., and Harrod, J. P.: J. Clin. Endocrinol. **10**: 1547, 1950.
62. Masters, W. H.: Gerontology. **8**: 33, 1953.
63. Masters, W. H.: Obst. & Gynec. **8**: 61, 1956.
64. Crossen, R. J., and Hobbs, J. E.: J. Missouri M. A. **32**: 361, 1935.
65. Allen, E.: J. A. M. A. **114**: 2107, 1940.
66. Gusberg, S. B.: Am. J. Obst. & Gynec. **54**: 905, 1947.
67. Korenchevsky, V., and Hall, K.: J. Path. & Bact. **50**: 295, 1940.

Discussion

DR. ALLAN C. BARNES, Cleveland, Ohio.—The presentation can be divided into four parts. In the first, the author surveys the panglandular status of the postmenopausal woman and points out that the failure of the ovary is the only significant endocrine change of these decades. In the second, he considers the metabolic alterations peculiar to the postmenopausal years and presents evidence that the effects of the ovarian failure are, by and large, undesirable. Although these two conclusions are not new, Dr. Masters presents them well and I doubt that anyone in the room would debate them violently. Certainly I shall not.

In the third portion of his argument, Dr. Masters advances a program of postmenopausal steroid management for the control of these metabolic changes. He advocates the 20-1 testosterone-estrogen ratio suggested by Shearman and his co-workers, as well as by others, to avoid the endocrine and metabolic dangers of unopposed estrogenation.

In the fourth part of his paper, the essayist outlines the prerequisites for a steroid which would sustain the postmenopausal woman without threat of harm. Certainly I would not dispute the need for a Utopian steroid such as he outlines, and information on its use would have been welcome news to all of us. This section of his paper, however, would have been strengthened considerably if it could have included solid figures and case reports. But by not bringing us such specific data, Dr. Masters transfers his presentation into the realm of the review type of paper. As such, it must complete with Stoddard's survey of the postmenopause, Rogers' excellent review of the menopause, and Shelton's persuasive defense of continuing and eternal steroid therapy.

While each of these review papers could be said to possess some advantages over the review which Dr. Masters has given us today, he still has one imperative advantage which distinguishes his summary—much of the work he reviews here was originally his own contribution. While one may be disappointed that he did not bring us specific figures today, it is well to remember that he has been responsible for many of the studies in gynecologic gerontology he is here discussing.

The thesis that the sex steroids should be administered routinely to all women after the menopause has been advanced repeatedly in the past decade and has been debated with vigor. With our increasing understanding of the degenerative changes of age, abstract logic seems to favor the proponents of such a course. But before one could anticipate general acceptance and widespread application of this procedure, carefully controlled series of women followed for prolonged periods must be adduced.

For the record, I should perhaps note that there are a few points at which I disagreed with the essayist's facts. Thus, I do believe there is acceptable historic evidence that the age at which the menses cease has advanced over the centuries. Thus I am inclined to believe

the work of Pincus and his co-workers on the declining androgen output in both women and men in the latter decades casts some doubt on his statement that "There is every evidence that the adrenal . . . continues mature secretory function essentially independent of the aging process." But these are essentially minor points and do not alter my acceptance of his fundamental thesis. Arguments against this thesis will abound for many years, but the opportunity which the gynecologic gerontologists are presenting to us is the opportunity to practice true preventive medicine.

DR. C. LEE BUXTON, New Haven, Conn.—Dr. Masters' and Dr. Randall's interesting discussions of the hormone changes which occur during the process of aging have brought into sharp focus an area in our gynecologic thinking which has in recent years been discussed frequently but as yet indecisively. This is the area of questioning as to whether or not the menopause represents a complete cessation of ovarian function with senility of ovarian tissue. On the one hand, there are those who believe that, following the menopause, the ovary might as well be dead and buried, that it has fulfilled its function in life, and that the human female is so constructed that she has physiologically adapted herself to this hormone change so that either other glands take up the slack and provide whatever sex steroid maintenance may be necessary, or that at this stage of life the human female can maintain her physiologic integrity without sex steroid function anyway. On the other hand, there are those who believe that the ovary, even though it does no longer ovulate, still produces some kind of ill-defined hormone stimulus necessary to maintain the female's sexuality.

Dr. Masters' discussion presents what may be considered a third attitude concerning the menopause, i.e., that although the ovary may cease its ovulatory function and may with some irregularity and variability gradually cease also its sex steroid secretion, this repudiation of sexual responsibility on the part of the ovary is a pathologic and not a physiologic one; that therefore possibly the menopause is a pathologic process and that postmenopausal life is hormonally pathologic and needs replacement therapy.

This is an interesting concept upon which Dr. Masters has, as we all know, been working for some time, and one cannot help but be most impressed by his clinical experiments concerning sex steroid replacement in elderly women with frequent resultant physiologic and psychologic rehabilitation. Furthermore, Dr. Masters' discussion of the protection of the aging female by sex steroids against protein imbalance and the exhaustion of calcium storage with resultant osteoporosis are factors which demand our most serious consideration.

On the other hand, the expression "neutral gender" used to identify the postmenopausal woman is one which is a little hard for me to get used to because it seems to me, sex steroid or no sex steroid, the postmenopausal woman may be just as intrinsically feminine as she was in her premenopausal years, although I am sure we would all be willing to agree that menstruation and reproductive potential are some of the basic elements of femaleness as such. I would like to submit the idea, for your and Dr. Masters' consideration, that possibly a beneficent nature has teleologically arranged by some kind of an unexplainable evolutionary process that the human female becomes nonreproductive in what is now known fairly realistically as "middle age." Were the human female able to reproduce well on into old age, as are the other menstruating anthropoids, there might be an even greater cry of distress on the part of both sexes of the human race than there is at the present time concerning the menopause, even including all its implications in the process of aging. It may be that the human nervous system is so constructed that it would have difficulty coping with the problems of reproduction after the age of 50.

Therefore, possibly the only area wherein I might be inclined to disagree with Dr. Masters' very interesting concept is a philosophic one. He apparently believes that the menopause is a pathologic process, which immediately places it in a category of a disease requiring therapeutic measures, specifically of sex steroid replacement. I believe the menopause to be a process of irrevocable physiologic aging which need not necessarily in any other respect than reproductive potential prevent a female from remaining a female, if she so desires.

In our less serious moments and in a less formal environment, I have accused my friend, Dr. Masters, of being a twentieth century Ponce de Leon who has not only searched for but possibly found a steroid fountain of youth. In both our serious and nonserious discussions, however, I readily confess to being most impressed by his thought-provoking investigations of this subject, and I hope that he, as a very able protagonist of an interesting concept, will continue his pursuit for the answer to this problem.

DR. HOWARD W. JONES, JR., Baltimore, Md.—I wish to spend my three minutes in remarks about the term "neuter gender," and I trust that these remarks will in no way tend to detract from the very great importance of the question raised by Dr. Masters. Gender is, after all, a very complicated state characterized not only by adult steroids but by many other things. It can be defined in terms of chromosome arrangement established at the time of fertilization. It can be identified in terms of the anatomy of the gonad. It can be defined in terms of the morphology of the external genitals. It can be defined in terms of the morphology of the internal genitals. And it can be defined in terms of society's attitude toward the individual and the attitude the individual assumes to society. Actually, from a chronologic point of view, the adult steroids are the last contribution to gender, and the gender may be quite feminine, even in the absence of the adult steroids. For example, in the syndrome of gonadal dysgenesis (Turner) the gender with respect to internal and external genitals is feminine but most of these patients are genetic males and furthermore have never been exposed to an adult steroid hormone and yet have a clear-cut social attitude, which is entirely feminine. Gender is therefore quite a complex matter and I wonder if the normal menopausal state could not be more accurately defined in other terms.

DR. S. LEON ISRAEL, Philadelphia, Pa.—Before asking Dr. Masters the two questions I have in mind, I wish to comment on "neutral gender," to which Dr. Buxton and Dr. Jones have so cleverly alluded. I do not think either one of them mentioned, although they implied, the psychological reference to neutral gender. One need think only of cartoons of the elderly Col. Blimp or of the men sitting in the window of their club on Fifth Avenue in New York whose heads are turned at any age by the swish of a petticoat or the turn of an ankle. I do not think the term "neutral gender" is a useful one, at least psychologically.

The two questions are perhaps somewhat unfair. Dr. Masters has in his previous writings referred consistently to the intramuscular injection of these steroids, and my first question would be whether he is now able to tell us that he has an oral substance affording a 20-1 ratio. Second, he has had an opportunity in 500 women to discern changes in libido with testosterone administration over a period of time and will he tell us about that.

DR. ARTHUR T. HERTIG, Boston, Mass.—I would like to ask whether Dr. Masters would distinguish in his therapy for all postmenopausal patients between the group that has some estrogenic function, as so beautifully shown by Dr. Randall, and the group which apparently has none.

DR. MASTERS (Closing).—In answer to Dr. Barnes: The most revealing statistics we have on the 65 year age group are projected in terms of the concentration of this group in our society as of 1960. This age group will comprise approximately 10 per cent of our total population early in this decade. While I thoroughly agree with him that there is historical evidence of the lengthening of the climacteric, I think that this is a relative rather than an actual increase in ovarian physiological activity. When the female's average life expectancy was 47 years, only a half-century ago, it was inevitable that the true climacteric age was in doubt. Actually, the onset of the menopause was placed with common approval as occurring somewhere in the early forties. However, since the female's life expectancy has exceeded 55, there has not been the slightest evidence of lengthening of the expected time interval of the onset of the climacteric. Thus, I think that the shift from the early to the late forties is actually only an expression of the greater life expectancy, and a resultant clearer definition of the actual onset of the menopause, rather than any physiological increase in ovarian secretory activity.

I agree with Dr. Pincus' work on the slowing of adrenal activity in the aging group. This is, however, another example of a comparison of relative secretory activity. While measurable adrenal activity does slow in the 70 to 80 year age group, this gland still shows the most active secretory function of the entire endocrine system. Actually, this secretory activity is much in excess of basic body metabolic need for this age group. Its excessive and unopposed catabolic influence is of major concern to students of the aging process. If we supplement the obvious sex steroid inadequacies exogenously, the adrenal shortly returns to normal physiological function.

I have often wondered if the slowing of adrenal activity in the aged is not an example of "work-hypertrophy" exhaustion. In most individuals of this 70 to 80 year age group, the adrenal secretory activity is so uniquely in excess of physiological demand that its catabolic influence is, as mentioned, of grave concern. Thus, this relative slowing of secretory activity may simply be a protective body mechanism, a defense really against adrenal catabolism. Obviously, there is no real evidence to support this purely personal opinion. It will remain for time to provide adequate support or to reject this theory.

In relpy to Dr. Buxton: I am in complete agreement with Dr. Randall's stated belief (so nicely presented in the preceding paper) that ovarian secretory activity continues after the menopause. I certainly do not think that the menopause represents a pathological state. It has been with us a long time as a physiological entity, and actually has only been reasonably understood in recent years.

Only in the last hundred years has our increased life span focused our attention specifically on the postmenopausal era. I do emphatically consider this phase of involution a pathological state—from a humoral point of view alone. While it is true that ovarian secretory activity continues after the menopause, it is equally obvious that this activity is inadequate in most cases to protect the individual against protein wastage, calcium imbalance, senile mental involution, etc. In short, evidence of continued ovarian activity in no sense presumes that the secretory activity of the ovary is sufficient to maintain an adequate physiological body economy. When we observe evidence of complete reversal of many of the senile physiological processes by the simple expedient of satisfying, exogenously, the obvious sex steroid starvation state, we are compelled to defend this position.

May I reply to the general discussion as a unit: Obviously, there has been more than a little expressed interest in the use of the term "neutral gender." This term has been developed in an attempt to express, succinctly, the entire concept of sex steroid insufficiency, unfortunately so closely associated with the aging process. If we do not use something to hang our hats on, we have difficulty in defining our case. I do agree with the possible psychological effects, and the theoretical distress associated with the term, and described by the discussants. We would be happy to use another equally effective term. However, the discussants should be made aware of the effectiveness and the drawing power of this coined phrase. "Neutral gender" as a term has demonstrated more than just the ability to occasion discussion on a theoretical plane as to its etiological correctness. This term has demonstrated a drawing power (on a purely professional level) far beyond our wildest expectation. Of the first one thousand inquiries from physicians received subsequent to the professional publication of various parts of this basic investigative program, only 15 asked for information in the field of estrogen-androgen, or sex steroid replacement, in the aging individual. The remainder of this huge professional cross-section asked for information to aid in the care or support of the "neutral gender." Thus, it is obvious that this term has been used to direct the interest of the medical profession to what we believe is the greatest unexplored field in medicine today.

Dr. Hertig has asked the most difficult question to answer. It is virtually impossible to delineate, in the individual patient, exactly how early therapy should be given. In the more advanced cases of mental or physical senility, the indications are obvious. I can give you this basic statement of policy: With this type of combined steroid replacement technique, it is virtually impossible to overtreat. If the patient shows any of the previously described symptoms of early senile mental involution, or if there is any evidence of early protein wastage or calcium imbalance, therapy should be immediately instituted.

The question of the use of oral medication rather than the parenteral route has been raised by Dr. Israel. There are an increasing number of advertised 20-1 steroid combinations which consist primarily of methyl testosterone and the estrogenic preparation being promoted by the individual pharmaceutical concern. A word of caution is in order here. It should be remembered that all of the steroid combinations have different absorption rates from the gastrointestinal tract. Since practically all of the drug firms use methyl testosterone as the oral androgen, we have only to remember that this steroid is approximately 50 per cent absorbed from the gastrointestinal tract. With the great variety of estrogenic preparations presently on the market, we have quite another problem on our hands. The absorption rates for estrogenic-type steroids vary from an approximate 50 per cent for sodium estrone sulfate, for example, to over 90 per cent for estinyl estradiol. It is for this reason that we emphasize repeatedly that the 20-1 combined testosterone over estrogen ratio must be a ratio of the absorbed steroid—not a simple bottle label.

As a side issue, but of some practical interest, our present long-acting steroid combinations for parenteral injection are less expensive than the oral 20-1 combinations, when we consider that maintenance of reasonable steroid balance may necessitate only an intramuscular injection every two to four weeks.

VAGINAL DYSPAREUNIA*

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ONE of the most important symptoms in gynecological practice is dyspareunia, seldom volunteered by the patient, often overlooked by the physician, and sometimes ignored after it has been mentioned. I have found that many new patients whose chief complaint was something other than dyspareunia failed to include it in the history but freely acknowledged it when questioned.

This presentation has no reference to supravaginal pathology in the pelvis and deals with vaginal lesions only, exclusive of congenital absence of the vagina. Neither are cases of dyspareunia and primary frigidity due solely to psychosomatic causes, which have recently been well discussed by others, included. It is based on experience with 70 patients in my private practice over a long period of years. Developmental deficiencies in the vagina, inadequate space at the introitus following an overenthusiastic perineorrhaphy or episiotomy repair, a hypersensitive cicatrix in the fourchette resulting from a "dashboard" perineal operation, and exaggerated postmenopausal contractions are all responsible for varying degrees of dyspareunia. Unrelieved discomfort and pain soon give rise to vaginismus, the initiation of a fear complex, and secondary frigidity, all of which may be the cause of serious domestic unhappiness and even lead to divorce. The necessity for prompt and early recognition and treatment of these lesions before the psyche becomes irreversibly disturbed is self-evident. Experienced gynecologists appreciate that the evaluation and treatment of the patient as a whole, with special reference to her mental attitude, sex life, and domestic tranquility, are just as important as the physical examination and local and operative therapy.

TABLE I. INDICATIONS FOR PERINEOTOMY AND APPLICATION OF GLASS VAGINAL OBTURATOR

Premarital	4
Brides	31
Perineal postoperative stenosis	12
"Dashboard" perineum	5
Remarried widows	4
Postmenopausal stenosis	10
For diagnosis or treatment	4
Total	70

Among the 70 patients (Table I) there were 4 premarital young women and 31 brides who had a distinctly miniature vagina with a tough, unyielding hymenal ring, usually situated a little above its normal location; 12 whose previous perineorrhaphy had unduly narrowed the vaginal introitus; 5 whose

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previous plastic repair had resulted in a "dashboard" perineum, consisting of skin, mucous membrane, and hypersensitive scar tissue, without proper restoration of the perineal musculature; 4 widows who had formerly enjoyed a normal married life and had remarried after several years of celibacy, only to discover that painless coitus had become impossible because of the intervening vaginal contraction; and 10 happily married women who developed dyspareunia caused by progressive atrophic changes in the canal after the menopause.

All of these patients were treated in the same way, with a simple perineotomy, plus a preliminary hymenectomy when necessary, and the insertion of a glass vaginal prosthesis for the duration of wound healing. In 4 additional cases the perineotomy was essential to afford access to the upper vagina in elderly women. In a few instances other indicated operative procedures, such as repair of a rectovaginal fistula, hysterectmoy, removal of rectal polyps and hemorrhoids, and curettage were carried out at the same time.

Three of the unmarried women, aged 21, 22, and 25, had primary amenorrhea due to endocrine imbalance, with developmental stenosis but no true aplasia of the vaginal canal. Absence of menstruation had evidently not concerned them until they contemplated marriage and their failure to seek earlier medical advice is difficult to understand. The other patient, aged 42, had menstruated regularly and discovered her difficulty only when she tried an experiment for the first time before an anticipated marriage.

Three operations were done on brides within the first week, 4 within the first two months, 5 between two and six months, and 13 between six months and five years. On the other hand, 6 delayed corrective treatment for from five to fifteen years. All of the women who presented themselves within six months were less than 28 years old, except one of 40 and one of 56. Three of them had had ineffectual premarital "stretching" by their physicians. This group presented no particular psychological problems and soon adjusted themselves to a satisfactory response after the use of the obturator was discontinued. This was also true of 7 of the 13 patients who postponed seeking advice between six months and five years, who were less than 27 years old. Four others were 35 or more and confessed that although they no longer had dyspareunia, coitus was a matter of more or less indifference to them. There were 6 patients who delayed consultation for five or more years. One had left her husband after a few days and another after four years, and then decided to remarry. Another, who had had two cesarean sections, although penetration had never been complete, was on the verge of divorce because of fourteen years of dyspareunia.

Twelve women were operated on for dyspareunia after a previous perineorrhaphy, which resulted in too much narrowing of the vaginal orifice, so that it would not accept two fingers without marked discomfort. They varied in age from 24 to 48 and had suffered in silence for from four months to twenty-nine years. Five patients who had been freee from discomfort before a previous perineal or episiotomy repair had an extremely hypersensitive cicatrix in the fourchette, due to the operator's failure to reconstruct the perineal musculture. Excision of the scar tissue, reapproximation of the muscle fibers, and the application of an obturator for four weeks afforded complete relief. It was with the utmost difficulty that 3 of these patients who had had an episiotomy were dissuaded from bringing a malpractice suit against their obstetricians.

Four attractive women had lost their husbands by death when they were about 40. After ten or twelve years of abstinence from coitus and an intercurrent menopause they had remarried, and were distressed to find that as a result of the long lack of dilatation, and incidental atrophic menopausal changes, the vagina had so contracted that painless intromission was impossible. This small group wasted no time in submitting to the necessary corrective procedure.

Why some postmenopausal women, still leading an active married life, should be subjected to pronounced contractural changes after the climacteric, while the majority are not, can probably be explained on the basis of individual endocrine peculiarities. There were 10 such patients, varying in age from 47 to 62 years, with the insidious onset of dyspareunia as early as six months and as late as ten years after the cessation of menstruation. Four of them had had a perineorrhaphy and one a vulvectomy many years before, but the end result of these operations had never caused them any inconvenience.

In 4 instances it was essential to perform a perineotomy to afford access to the upper vagina in elderly women: one for primary carcinoma of the upper third of the vagina, one for a fibroid prolapsed through the cervix, and 2 for the application of radium.

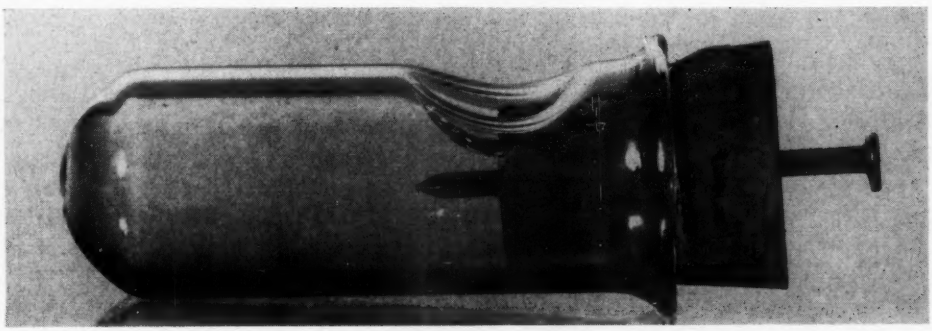


Fig. 1.—Vaginal obturator fitted with cork and nail.

A simple perineotomy is done by incising the perineum and posterior vaginal wall longitudinally, after a hymenectomy if necessary, just enough to permit the easy introduction of two fingers, and suturing the fourchette transversely with interrupted 20 day catgut stitches. In case of a "dashboard" perineum, the sensitive scar tissue is also excised and the vaginal fibers of the levator ani muscles approximated. A Pyrex glass obturator of appropriate size, with a little notch just above the flange to prevent pressure on the overlying urethra, is prepared, by plugging the open end with a cork, through which a short nail with a flat head has been inserted. The nailhead is allowed to project about 1 cm., which helps to maintain the obturator in position when it is caught in a small buttonhole in a T binder (Fig. 1). During the first postoperative 24 hours the obturator is removed and replaced by the resident or nurse. The patient is allowed to sit on an inflated rubber ring in a chair on the second day and encouraged to practice reinsertion herself thereafter. After three more days of walking in the hospital she becomes accustomed to the presence of the foreign body and is allowed to go home, with instructions to wear the device continuously for two weeks. When the wound has healed it should be worn at night for another two weeks. Coitus should not be permitted until all soreness on bimanual examination has disappeared, but should then be resumed. By this time the patient has demonstrated to herself by the

repeated insertion of the obturator that vaginal dilatation will not excite discomfort or pain, and subconsciously realizes that she no longer need fear dyspareunia. Apprehension of approach and vaginismus are thus completely eliminated. In all the patients treated the results have been satisfactory. One can only surmise how many physicians must have seen a number of these patients without discovering that they were suffering from dyspareunia and detecting its cause.

Conclusions

Dyspareunia is frequently due to developmental deficiencies in the vagina, inadequate space at the introitus after perineal operations, and exaggerated menopausal stenosis. It is a symptom seldom volunteered by the patient and frequently overlooked by the physician. Early recognition and prompt treatment of these lesions before the psyche becomes irreversibly disturbed are important. Premarital "stretching" of the vagina is of little value. When doing perineorrhaphy or episiotomy repair the operator should make sure that the vaginal orifice will easily accept two fingers after the last suture is tied. The essentials of treatment are a simple perineotomy and the application of a Pyrex glass vaginal obturator for one month. The end results have been entirely satisfactory with complete elimination of dyspareunia in 70 cases.

580 Park Avenue

Discussion

DR. JOHN PARKS, Washington, D. C.—Dr. Dannreuther has selected from his extensive gynecologic practice 70 women who had dyspareunia as their main problem. He has emphasized that the patient seldom volunteers information about marital dystocia as her primary reason for gynecologic examination. As her history unfolds, however, frequently it is found that she has suffered in silence and that she has lived without satisfaction in an unhappy household. Often a minor anatomic defect becomes a major family concern.

When as a part of premarital examination the hymenal opening is found to be small or when the introitus of a married woman does not permit the introduction of two fingers with ease, it is advisable to bring up in private interview the question of possible dyspareunia.

One half of the patients presented were listed under the headings of "premarital" and "brides," and they are important patients in office practice. Except when the hymenal tissue is very thick and unyielding, premarital dilatation of the hymenal ring seems to be a less painful and more physiologic procedure than perineotomy. Satisfactory dilatation can be accomplished with a well-lubricated cone-shaped Kelly rectal dilator graduated from 20 to 50 mm. in diameter (Fig. 1). The patient is shown how to use the dilator and is instructed to stretch the vaginal opening twice daily for two weeks prior to marriage. This procedure is very simple, easy, and practically painless, and results in satisfactory preparation of the hymenal opening.

A delay in proper preparation of the introitus for marriage varied from one week to fifteen years in patients listed as brides. In the presence of dyspareunia psychosexual adjustments to marriage are seldom improved with time. Although one of the patients referred to Dr. Dannreuther had had two pregnancies terminated by cesarean section, she still had a virginal vaginal opening. This demonstrates the extent to which anatomic dystocia may be overlooked.

The practical addition of a cork and nail to the obturator provides the patient with a much better means of controlling manipulation of the dilator. One of the problems of using plain glass dilators is the ease with which they are dropped and broken on modern tile floors and porcelain bathroom fixtures.

Vertical perineotomy with transverse closure is usually a very satisfactory method of enlarging the introitus. However, there are times when extensive scar tissue has to be removed, leaving a defect which is better closed by Z-plasty. This principle of correcting skin contractures in plastic surgery permits greater lengthening of the new scar than does a single incision.

In patients with postmenopausal vaginal constriction the use of an estrogen-containing ointment or cream in addition to the obturator has the advantage of giving pliability to partially devitalized tissues.



Fig. 1.—Kelly dilator graduated from 20 to 50 mm. in diameter. (Made by Dittmar and Penn Corp., Philadelphia, Pa.)

DR. MILTON L. McCALL, New Orleans, La.—Dyspareunia is a symptom complex about which very little appears in current medical literature or in gynecologic textbooks. Dr. Dannreuther has pointed out that while it is a symptom of great importance to the seasoned gynecologic clinician who makes special effort to ferret it out, it is frequently overlooked or ignored by others. He has strongly implied that increased vigilance by the physician toward the diagnosis of this condition would be rewarded by the prevention or early alleviation of much mental and physical anguish.

The author has chosen to exclude all patients with pathology above the level of the vagina; in fact, his cases deal almost entirely with dyspareunia resulting from narrowing of the vaginal introitus. There were 17 patients whose symptoms followed some type of vaginal surgery. The author obtained excellent results by utilizing perineotomy or the necessary plastic repair of the "dashboard" type of perineum.

While outlet dyspareunia is of great importance, in my experience there is an additional small group of patients in whom uncomfortable coitus occurs because of abnormality of the upper vagina. This may be seen following traumatic vaginal delivery with extensive laceration and subsequent contractural changes in the vaginal fornices, or following manipulation for criminal abortion or the deposit of corrosive chemicals into the vagina, such as potassium permanganate. However, by far the most important cause perhaps is the change in the anatomy of the upper vagina which so often follows vaginal

surgery performed for some degree of uterine prolapse with associated enterocele. It is upon this group that I should like to center my few remarks. There are two main factors which cause dyspareunia in these patients: (1) shortening of the vagina, and (2) narrowing of the vaginal vault. Either or both of these frequently brings about marked discomfort during coitus because of the unyielding area produced.

It is well known that even the most expert gynecologic surgeon may find it necessary to narrow the upper vagina during surgery in order to prevent recurrence of enterocele.

In recent years I have used increasingly a technique which I call "posterior culdeplasty." This is a technique usually performed at the time of vaginal hysterectomy which brings about obliteration of the redundant cul-de-sac of Douglas and suspends it to the uterosacral ligaments which are brought together in the midline. This is accomplished by a series of internal sutures and two or three through-and-through sutures which are tied within the vagina. A modified Heaney technique is used in connection with this procedure so that no other structures are brought to the midline. The once relaxed cul-de-sac is therefore gathered into a sturdy shelf of tissue which serves to prevent the subsequent development of enterocele. In my hands this technique has insured the greatest vaginal length possible in any given case and, because no tissue is actually removed, there is usually less narrowing of the upper vagina than is seen with other techniques. This procedure is strongly recommended for the prevention of upper vaginal dyspareunia.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—I am moved to comment that the younger generation coming up is probably much more familiar with the word "high" than "dashboard," and I wonder if we should not give some consideration to change in terminology.

DR. DANNREUTHER (Closing).—I neglected to mention the simultaneous use of estrogenic vaginal creams which is helpful in menopausal women. I agree with Dr. Parks that there are many prospective brides with small vaginas whose hymens are sufficiently elastic to be little of a handicap, and require no treatment.

Dr. McCall's suggested technique for disposing of an enterocele with minimal narrowing of the upper vagina, which may cause dyspareunia, is worthy of trial.

A few weeks ago I was consulted by a bride of forty-eight hours in a highly tense and emotional state because of impossible coitus. Her husband had been assigned to a government post in a foreign city for a two-year term and they were to leave New York the next day. All I could do under the circumstances was to explain the situation in detail and give her the largest glass obturator the vaginal orifice would accept, with the suggestion that she use it until she could get further attention. In referring her to another gynecologist, I presumed to advise that a perineotomy be done. However, that my proposal was deemed of little value is evident by the following paragraph quoted from the letter of acknowledgment which I received recently:

> "Today on pelvic examination the hymenal ring admits two fingers but she has very tight, rigid perineal muscles. With some encouragement she will relax, but it will take some time. I thought perhaps of trying a local block with Novocain if encouragement does not help."

This difference of opinion speaks for itself and perhaps justifies my bringing this somewhat elementary subject to your attention.

THE NATURE AND DEVELOPMENT OF THE SO-CALLED GLANDS OF THE CERVIX UTERI*†

C. Frederic Fluhmann, M.D., San Francisco, Calif.

(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine)

A DEFINITE constancy prevails in current descriptions of the histologic appearance of the cervix uteri. It is invariably considered as a glandular structure composed of branching tubular glands of the compound racemose variety which are lined by columnar cells similar to those of the surface epithelium and without any specialized differentiation. The plicae palmatae, or folds of the mucosa of the cervical canal, are casually mentioned as a gross finding but without explanation as to their role in the development of the cervix or their influence on the structure of the individual glands. There is likewise no specific information regarding the time of life during which these structures appear, although they are often included in the general statement that at birth the glands of the uterus are represented by shallow depressions of the lining epithelium.

The writings of the second half of the nineteenth century, however, show that at that time the nature of the cervical glands was a controversial subject. Most authors described tubular glands as they are recognized today, but others entertained a quite different concept. Kölliker[1] in 1853, Tyler Smith[2] in 1855, and in succeeding years histologists such as Peaslee[3] and Satterthwaite[4] directed attention to the manifold rugae or folds, which are present in addition to the plicae palmatae, as an explanation for the formation of glandular structures. They believed that the cervical mucosa is thrown up into numerous columns which run in longitudinal, oblique, transverse, or curved directions and that the grooves between them form sinuous pits with a transverse diameter approximately corresponding to their depth. They were called "mucous follicles" or "open glands" in contrast to tubular glands. Tyler Smith[2] wrote that "besides the primary rugae, each fossa is seen to be subdivided by smaller rugae, from which curved septa, still more minute, take their origin, dividing the principal fossae into a great number of crypts arranged like a fine piece of network. In each of the fossae between the primary rugae, as many as forty to fifty crypts or laminae may be seen. A cervix of moderate size would show between the transverse rugae . . . alone . . . from two to three thousand follicular pits." Pouchet and Tourneux[5] in 1878 spoke of "diverticulae of the mucosa" and stated that a "distinction between depressions of this type and true glands has

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not been sufficiently established." Another group of investigators, notably Friedländer[6] in 1870, sought to reconcile the two schools of thought by recognizing the existence of both "open glands" and tubular glands but assigning their appearance to different periods of life. They believed that in the newborn and during the first 3 or 4 years of life only mucosal excrescences were apparent but that the gland apparatus became well developed by the tenth year of life. Nagel[7] felt that the cervical glands develop from depressions of the epithelium which appear as shallow furrows and not from the plicae palmatae. Robert Meyer[8] described a postnatal diminution of the "glandular indentations and papillae" of the cervix of the newborn and stated that they often then became transformed into small tubular lacunae.

The present report is based on a study of the cervix uteri of the fetus during the last trimester of pregnancy, of the newborn, and of infants and children up to the menarche, and shows that during this time there are no tubular glands present in the cervix uteri. Instead, a complicated pattern of exophytic folds and secondary outgrowths characterizes the mucosa and its maximal development is attained in the newborn. There is then a postnatal regression of these epithelial formations which persist until the menarche without any further radical transformation.

Procedure

This study is based on the examination of 82 specimens of the cervix uteri obtained from autopsy material. Of these, 15 were from premature babies weighing from 780 to 2,640 grams, or approximately from the twenty-sixth to the thirty-seventh week of gestation. Twenty-eight were from newborn babies at term, either stillborn or who died within a few days after delivery. The infants and children were represented by 39 specimens, of which 10 were from the ages of 2 weeks to 3 months, 6 from 3 to 6 months, 6 from 6 months to one year, 4 from one to 2 years, 7 from 2 to 5 years, and 6 from 5 to 14 years. Of the latter, there were one at 5½, one at 6, one at 7, one at 11, and 2 at 14 years. The 2 14-year-olds had reached the menarche within one year prior to death but examination of the ovaries suggested that the menstrual cycles had followed an anovulatory pattern. There were many causes of death but they were not considered as factors which interfered with the normal histology of the cervix uteri.

The specimens were examined from conventional hematoxylin-eosin microscopic preparations and from relatively thick (0.5 to 2 mm.) sections cleared in xylol and oil of wintergreen. A number of representative sections also were stained with periodic acid-leukofuchsin to permit study of the secretory activity of the epithelial cells.

The sections for clearing were cut freehand with a razor blade but before staining it was necessary to prepare the tissues in order to make them firm and easy to manipulate. Fresh tissues were fixed in formalin, washed in water, and dehydrated in ethyl alcohol, 70, 80, and 95 per cent, and absolute alcohol. After sectioning they were then hydrated by running through the same solutions in the reverse order. Most of the material employed was obtained from paraffin blocks so that it was necessary first to dissolve the paraffin blocks with xylol and then hydrate by passing through the alcoholic solutions before staining. The staining was done lightly by immersion in Mayer's hematoxylin 1 per cent. The fixation and clearing were then accomplished by placing the sections for from twenty-four to forty-eight hours in ethyl alcohol, 70, 80, and 95 per cent,

absolute alcohol, xylol, and oil of wintergreen. They were kept in mineral oil and examined in oil under a stereoscopic microscope. The photomicrographs of the cleared specimens accompanying this article represent magnifications varying from 6 to 12 and were chosen merely to give the most favorable appearance.

The Fetal Cervix During the Last Trimester of Pregnancy

One of the characteristics of the epithelium of the fetal uterus is its property of proliferating and forming folds which extend in various directions. At first they are found in both the fundus and the cervix, but later they disappear from the body of the uterus. In the cervix, however, they persist and expand so that the more pronounced eventually become grossly recognizable as the plicae palmatae. They extend not only in a longitudinal but also in a transverse and oblique direction, and they play a fundamental part in the formation of the so-called glandular structures of this organ.

Hunter[9] reviewed the role of mucosal folds in the cervix uteri of the early fetus and stated that "the uterine segment of the single median genital canal at first appears in transverse section as a tiny circle surrounded by cubical-shaped epithelial cells. With the growth of the part, the circle appears to elongate in a lateral plane and forms a transverse oval with a narrow lumen. Then by a process of irregular growth, the walls of the oval become folded upon each other and the simple oval becomes a wavelike slit, somewhat like the letter W. Secondary longitudinal folds appear, and from these other smaller accessory folds arise." The uterus now elongates and there is a flattening of the folds in the endometrium. This flattening, however, does not occur in the cervical segment where the folds are more or less clearly retained. "Transverse folds are then added to these longitudinal folds, and as a result there are formed broad swellings which project into the lumen of the cervix and fill it. When this occurs the folds assume an oblique direction in an effort to accommodate themselves in the available space. These obliquely placed folds are developed in the 160-mm fetus." This fetal length corresponds approximately to the sixteenth week of gestation.

In this series there are 15 specimens of the cervix uteri obtained from the twenty-sixth to the thirty-seventh week of intrauterine life. The epithelium is composed of columnar cells of medium height with basal nuclei, although in 5 of the specimens from older children there are early secretory changes which presage the activity seen in the newborn at term. The configuration of the mucosa lining the cervical canal is seen as a continuation of the development of folds described in the fetus at 4 months (Figs. 1, *a* and *b*, 2, *a*, *b*, *c*, and *d*). These folds vary in size and number but apparently increase with increasing age. They are visible whether the sections are taken lengthwise or in cross-section so that they course in various directions—longitudinal, transverse, and oblique. The grooves or crypts which separate the folds vary from 1.0 to 3 mm. in depth and are obliquely placed indicating that in adapting themselves to the cervical canal they incline in the direction of the external os. At times an occasional fold becomes unduly pronounced so that in microscopic sections it has the appearance of a projecting mucous polyp (Fig. 1, *a* and *b*). The grooves or crypts in the past have been interpreted as tubular glands but the thick cleared preparations demonstrate that they are not round cylindrical structures but actual clefts extending at least through the thickness of the sections (0.5 to 2.0 mm.) (Fig. 2, *a*, *b*, *c*, *d*). There are also circular or oval formations deep in the mucosa (Fig. 1, *a*) which have been accepted as cross-sections of tubular glands, but they likewise should be considered as tangential cuts across the irregular grooves between the folds.

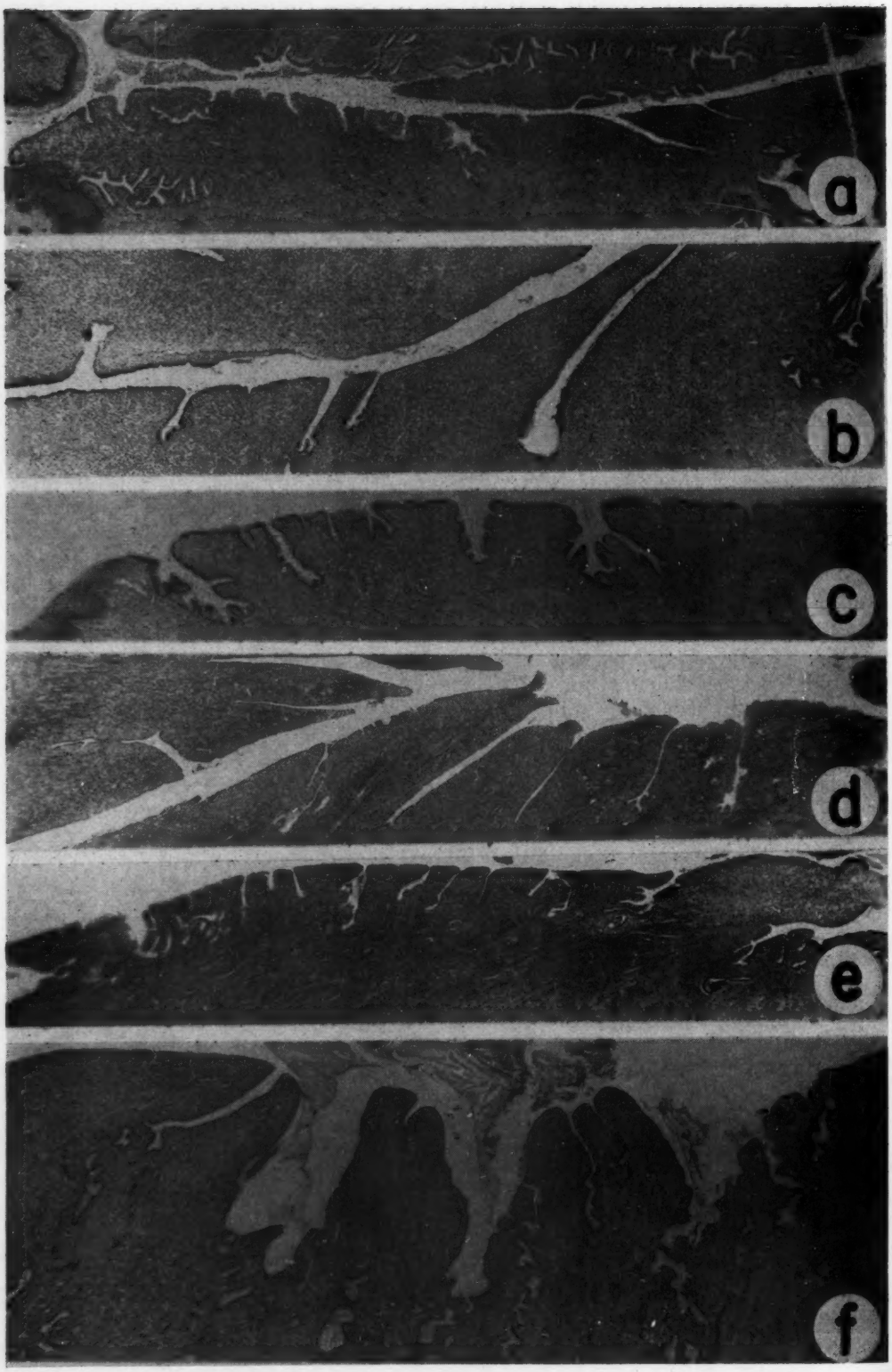


Fig. 1.—The cervix uteri of (*a*) premature baby at twenty-ninth week of intrauterine life, (*b*) premature at 32 weeks, (*c*) baby 2 weeks old, (*d*) infant of 2½ years, (*e*) child of 6 years, and (*f*) of 14 years. (×35.)

The Cervix of the Newborn at Term

The uterus before birth undergoes two growth phases.[10] The first lasts until the seventh month and is in accord with the general lineal increase of

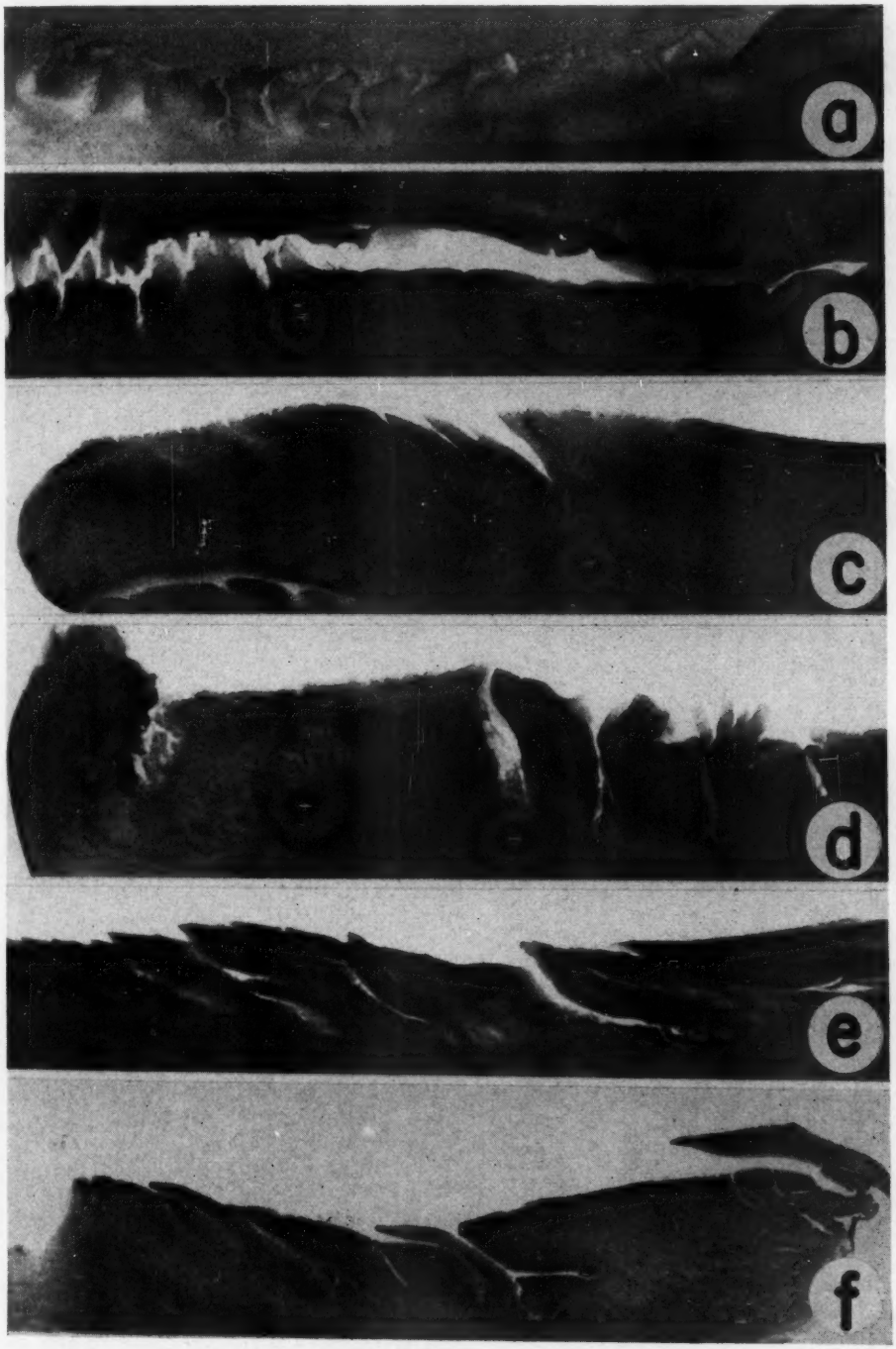


Fig. 2.—Thick, cleared preparations of the cervix uteri. (*a*) Premature baby at 27 weeks, (*b*) premature at 27 weeks, (*c*) premature at 31 weeks, (*d*) premature at 37 weeks, (*e*) child 4 years old, and (*f*) 6 years. Photographs of specimens immersed in mineral oil and taken with direct and transillumination.

body length. During the last 3 lunar months, however, there is a very marked augmentation in the rate of growth so that the uterus becomes much longer than would have resulted from the early fetal growth rate. This secondary growth increment manifests itself chiefly in the cervix, which at birth is much longer in relation to the length of the fundus than is found in the adult organ. In keeping with this process there is a very marked enhancement of both proliferation and secretory activity of the cells of the cervix and vagina. On the other hand, it is remarkable that there is no corresponding change in the endometrium, which is made up of relatively low cuboidal cells with occasional indentations which later become tubular glands. Although the cervical mucosa actively reacts to the maternal hormones, the endometrium fails to respond, a fact which is corroborated by the failure of these cells to stain with periodic acid-leukofuchsin.

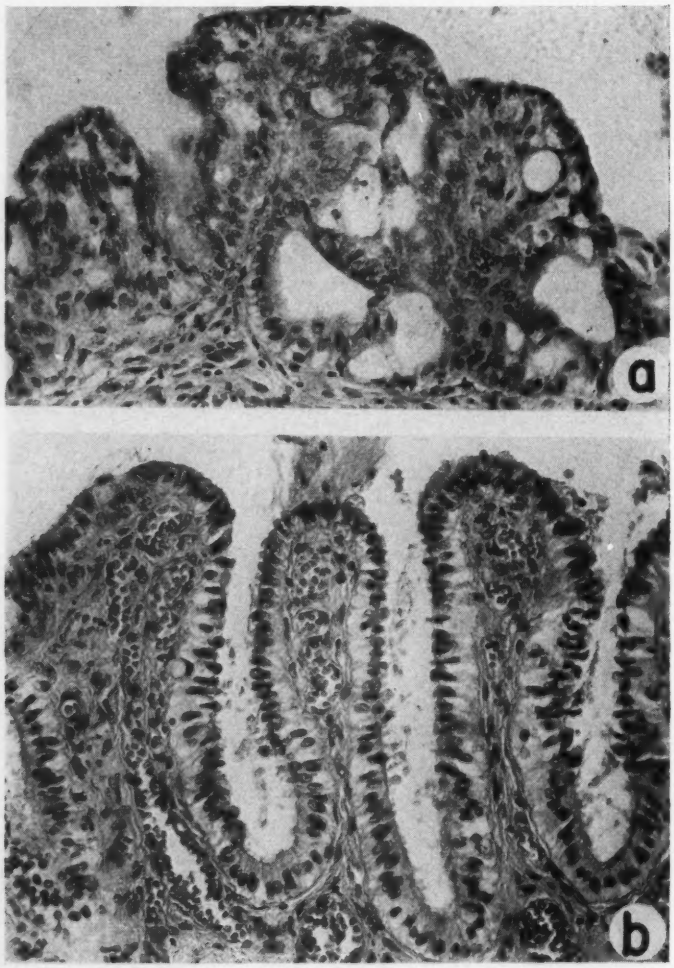


Fig. 3.—Newborn baby at term. (*a*) Area in one of the grooves between two folds of the cervix uteri, and (*b*) external os (congenital erosion). (×220; reduced ¼.)

The 28 specimens of the cervix uteri from newborn babies at term demonstrate this trenmendous proliferation and secretory activity. The individual cells now have become tall columnar units with the nuclei elevated to the middle of the cell (Fig. 3, *a* and *b*), and in periodic acid-leukofuchsin preparations the cytoplasm assumes a deep red stain which persists after digestion. There is a marked heaping up or vertical stratification of the cells, and here and there are

individual cells which are greatly distended with mucus and have eccentric nuclei flattened against the cellular membrane (Fig. 3, *a*). Epidermidization or squamous prosoplasia was seen in only 2 of the 28 cases, and a so-called "congenital erosion of the cervix" occurred in 6 instances.

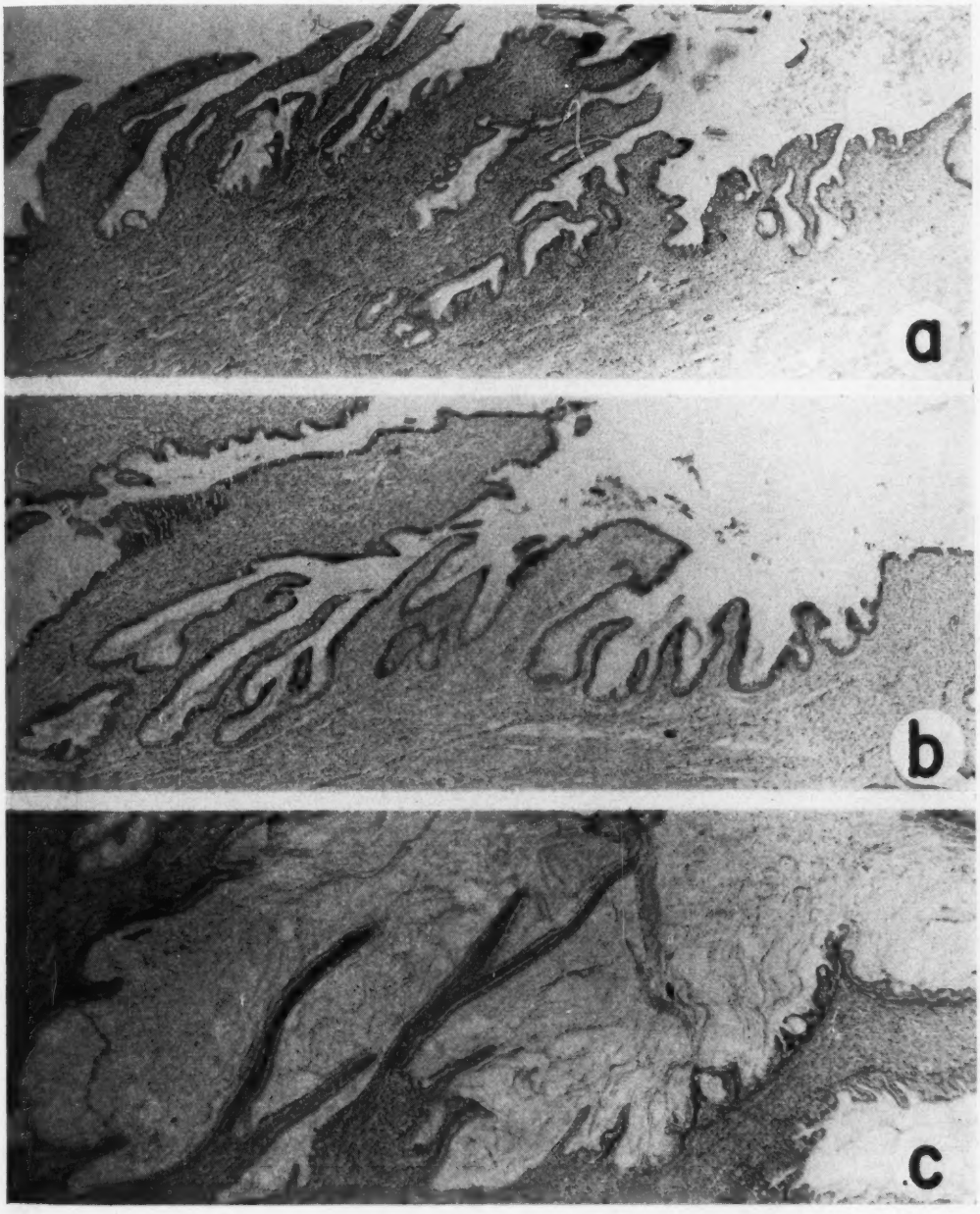


Fig. 4.—Cervix uteri of newborn babies at term. (×35.)

The mucosal folds of the cervix have now greatly increased in size and number and crowd into the canal (Fig. 4, *a*, *b*, *c*). Their surfaces in addition carry innumerable small and large papillary protuberances so that they appear as relatively long and short stems with multiple fine branches of varying lengths

(Figs. 4, *a, b, c,* 5, *a, b, c,* and 6, *a, b*). In other instances there are slender processes which jut into the canal and are seen either as thin partitions or fingerlike protrusions according to the thickness of the specimen (Figs. 4, *c,* 5, *b, c,* and 6, *b*). A transverse or tangential section has the appearance of a

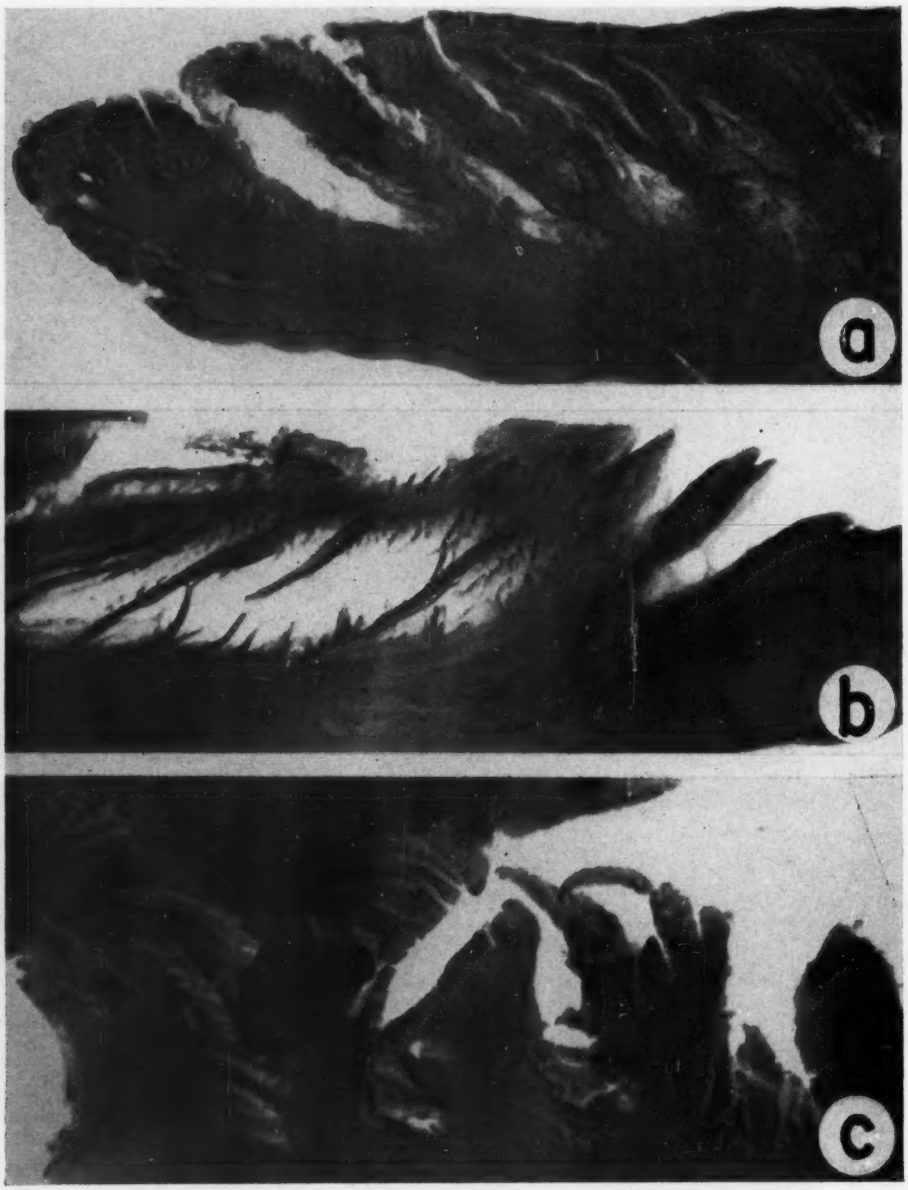


Fig. 5.—Thick, cleared preparations of the cervix uteri of newborn babies at term. Photographs taken with specimens immersed in mineral oil and with direct and transillumination.

honeycomb with oval or round compartments. The over-all effect of these changes is to produce irregular pockets filled with mucus secretion, and consequently to simulate to some extent the fundamental pattern of the cervix of the

mother at term. There are no demonstrable tubular glands, although conventional thin microscopic preparations show oval and round isolated cross-sections of the secondary folds and projections which suggest the presence of segments of such glands. These areas when associated with actively secreting cells and

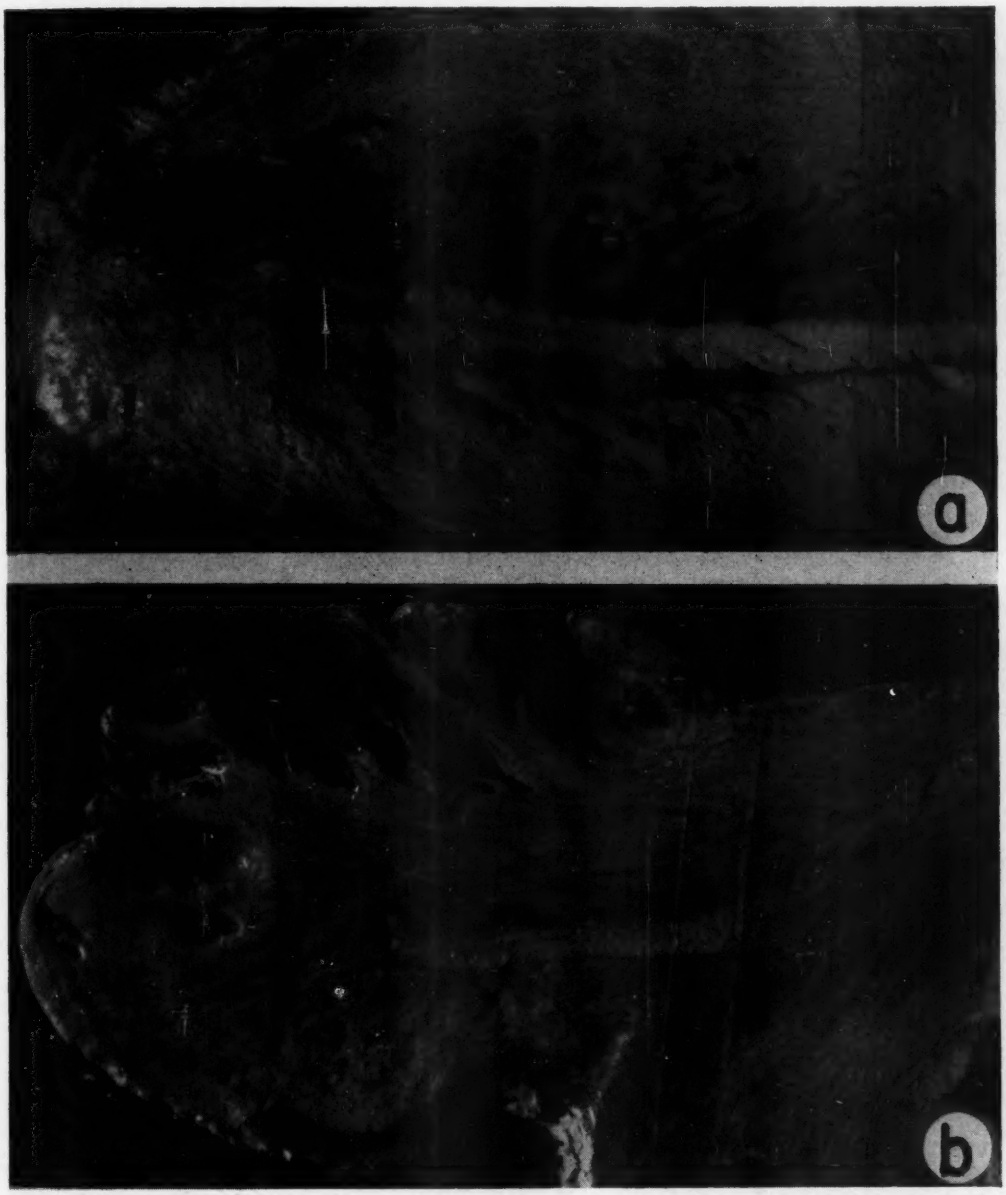


Fig. 6.—Two thick, cleared specimens of the cervix uteri of newborn babies at term. Photographs taken in air and with direct illumination.

large distended cells simulate the picture which has been described as "adenomatous hyperplasia" or "glands within glands."[11, 12] The papillary projections are of interest as they occur on relatively flat areas of the mucosa as well as on

the folds and are seen in erosions of the cervix where the columnar epithelium extends over the external os (Fig. 3, *b*). These structures were recognized by the older writers and described as "villi" or "papillae."

The Cervix During Infancy and Childhood

The augmented growth of the fetal uterus in the last trimester of pregnancy terminates at birth and during the first 5 months of life there is a gradual regression so that its length assumes the dimensions it would have reached had the early fetal growth rate been maintained.[10] This regression chiefly involves the cervix and there is a cessation of the secretory activity of the columnar cells

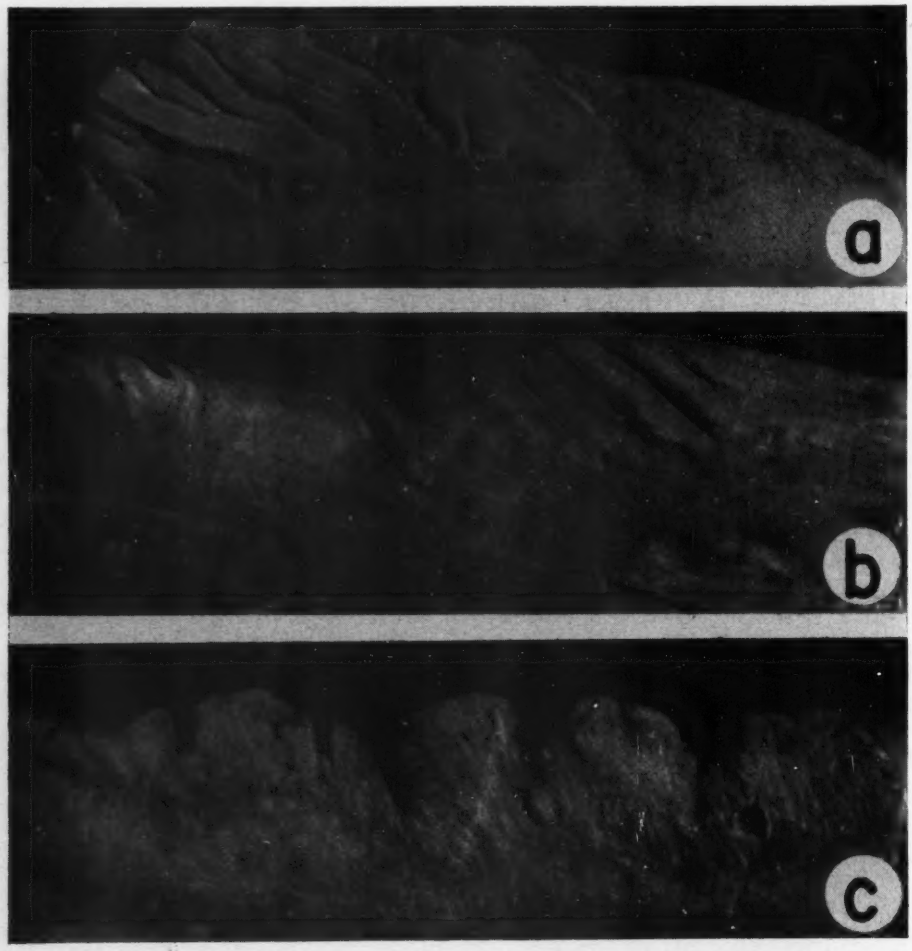


Fig. 7.—Thick, cleared specimens of the cervix uteri at (*a*) 4 months of age, (*b*) 2 years, and (*c*) 14 years. Photographs taken in air and with direct illumination.

which one month after birth have decreased to a medium size and only faintly stain with periodic acid-leukofuchsin. There is no evidence of a massive destruction of the cervical mucosa such as is described by Stieve[13] in the maternal cervix during labor. The larger folds of the cervix of the newborn, with their multiple secondary papillary outgrowths, persist to a diminished extent and form the basis for the general appearance of the cervical mucosa until the menarche. A congenital erosion of the cervix was observed in 6 cases, and epidermidization was noted only twice.

In this series there are 39 specimens of the cervix uteri obtained at ages varying from 2 weeks to 14 years. There are no instances of well-defined tubular glands extending downward from the surface and branching irregularly in the manner of racemose glands. The fundamental pattern remains of primary and secondary folds which have regressed from the maximal development attained in the newborn at term (Figs. 1, *c, d, e, f,* 2, *e, f,* and 7, *a, b, c*). These folds in many cases are very prominent and on section give the appearance of multiple polyps protruding into the canal in the direction of the external os (Figs. 1, *d, e, f,* 2, *e, f,* and 7, *a*). This same general conformation of the cervical epithelium is apparent in the 2 specimens from girls 14 years old who had menstruated during the previous year. The individual cells in these instances, however, are of a higher columnar type and approach the appearance of the "picket cells" seen in adults.

The Evolution of the Cervical Mucosa

The morphogenetic processes which lead to the formation of the various glandular systems of the body vary greatly and usually the cells concerned assume specialized and distinctive characters. A pertinent example is the evolution of endometrial glands, which is readily determined not only in uteri obtained at different ages before the menarche but in the reconstruction following the desquamation which accompanies menstruation. At first, either in the newborn or during the immediate postmenstrual stage, the glands are represented by tubular invaginations which run vertically from the surface to the base of the mucosa. These infoldings are closely associated with a highly specialized stroma which gradually increases in depth and as this proceeds the glands also increase in length. In time the prolongation of the glandular tubules become more rapid than the thickening of the stroma, so that they become tortuous and looped in order to accommodate themselves to the limited space. The individual cells lining the glands differ from those of the surface and undergo the characteristic specialization which enables them to react to the ovarian hormones. The stroma also is able to respond to endocrine stimuli and takes part in the changes associated with the menstrual cycle and gestation. Another peculiarity of this mucous membrane is the narrow basal layer adjoining the myometrium which does not respond to endocrine stimulation and acts as a source for regeneration of the tissues following their destruction.

The cervical mucosa presents a totally different picture. It must be considered as a functional structure since it does produce a secretion which varies in character and amount according to the endocrine stimulus. The cervical secretion plays an important role at various stages of the sexual cycle and during gestation it forms a thick gelatinous mass corresponding to the "mucus plug" of certain other species and serves to close the cervical canal. This particular function, however, is not necessarily attributable to specialized tubular glands similar to those found in the endometrium since it results from the activity of the individual cellular elements whether on the surface or along the grooves or crypts between the folds. There is also no specific stroma which develops as a corollary of the secreting epithelium, since the surrounding connective tissue has the same properties throughout the total depth of the cervix. Finally, there is no characteristic basal layer as in the endometrium.

On the basis of the findings in the present study it appears that in early life the arrangement of the secretory epithelium of the endocervix must be considered as resulting from two distinct influences:

1. There is first a definite evolutionary process, already apparent in the early fetus, which is characterized by a complicated system of longitudinal, transverse, and oblique folds of the mucosa and its underlying stroma. The

irregular pattern of these folds protruding into the cervical canal is the fundamental picture seen in premature babies, newborn babies, infants, and children before the menarche.

2. A secondary growth of the cervical mucosa, which begins in the later weeks of intrauterine life, is superimposed on this system of folds and grooves. It reaches its maximal intensity in the newborn at term, and then subsides to a varying degree during the first month after birth. It is the ultimate result of a reaction to the maternal hormones and affects all the cells of the mucosa. They become tall columnar units and attain a high degree of secretory activity so that the nuclei are elevated above the base and many large overdistended cells appear (''cellular cystic degeneration''). Along with this functional performance there is a great proliferation of the cells and as they increase in number they are thrown up into innumerable small protuberances varying from minute projections to actual papillae and fingerlike processes. These secondary outgrowths serve to expand the secreting area and occur not only along the folds but on the relatively smooth surfaces of the cervical canal. Their formation should be regarded as resulting from outgrowths of the epithelial cells carrying the underlying stroma with them, and not as primarily connective tissue projections with a covering of epithelium. They are a characteristic finding over the portio vaginalis in the well-known ''congenital papillary erosion.''

At this stage the two growth impulses, namely, the basic formation of folds and the added exophytic processes due to the intense proliferation of the covering epithelium, result in wide differences in the appearance of the cervical canal. The increased secretory activity which produces large amounts of mucus also contributes to the picture. There are probably no two specimens exactly alike, but my general impression is that there is an immature or incomplete attempt to reproduce the honeycomb-like agglomeration of pockets of mucus secretion which characterizes the cervix of the mother at term. This is seen in the cervix of the newborn either in areas between the larger folds (Figs. 4, *a*, *b*, and 5, *a*), in actual ''cells'' contained between fingerlike processes (Figs. 4, *c*, 5, *c*, 6, *b*), or in compartments enclosed by irregularly curved, thin partitions (Fig. 5, *b*).

With the birth of the baby and the disappearance of the maternal hormones there is a regression in the size and weight of the cervix uteri of the newborn. Although the weight and length are said to diminish over a period of 5 months the histologic regression of the epithelial cells seems to be complete in one month. By this time the signs of secretory activity have disappeared and the papillary projections have diminished in size and number. The cells become of a medium to low columnar type with basal nuclei; the characteristic ''picket cells'' of the adult cervix are not seen until after the menarche. The major mucosal folds, however, persist as the most characteristic feature of the preadolescent cervical mucosa, and they are accompanied to a greater or lesser extent by secondary papillary outgrowths.

The activation of the cervical mucosa in the baby at term further emphasizes its fundamental difference from the endometrium. It must be considered as additional evidence in favor of the theory advanced in 1954 before this Society that the endocervical epithelium is of urogenital sinus and not of Müllerian origin.[14] While the endometrium is quiescent, the responses of the cervix to the maternal hormones go hand in hand with related changes in the vaginal mucosa. The epithelium of the vagina becomes markedly hypertrophied, assumes its characteristic ''chicken wire'' appearance, and the cells are deeply laden with glycogen at the same time that the endocervical cells are actively secreting. The postnatal regression likewise occurs concomitantly in both the cervix and the vagina. It also may be of significance that the vaginal mucosa at this age is similarly involved in numerous folds.

The exact maternal hormones concerned in these processes is not known but it is probable that at least both estrogen and progesterone exert some influence. In some unpublished studies I have been able to reproduce excrescences and typical secretory changes in the cells of vaginal mucosa of the rat which are not unlike those seen in the cervix of the newborn human. This required the administration over long periods of time of a mixture containing a small amount of stilbestrol with relatively large proportions of progesterone and testosterone. At any rate, the production of the secondary outgrowths and marked secretory activity in the cervix uteri most likely are not pure estrogenic effects. On the contrary, in the human endocervix estrogen stimulates the prosoplastic changes which eventuate in epidermidization.[14, 15, 16]

These findings in the cervix uteri before the menarche are of importance in interpreting the histology of the adult cervix but are not necessarily directly applicable. A preliminary study of thick cleared sections of cervices obtained at gynecologic operations indicates that tubular structures may be present in the mature organ. However, they apparently are not complete branching tubules coursing from the surface to the base as maintained in the histologic descriptions of our current textbooks but represent fragmentary segments directed not only vertically but in transverse and oblique directions. Any explanation for their formation first must take into consideration the growth impulses manifested in the young which result in exophytic processes and not in invaginations of the surface mucosa. It is particularly significant that the picture in the newborn cervix of multiple folds and secondary outgrowths which result in the formation of pockets of mucus is of the same nature as that seen in the pregnant woman. The occurrence of adenocarcinoma in only some 5 per cent of instances of cancer of the cervix, the papilliform nature of many such adenomatous cancers, the rarity of benign adenomas, and the frequency of exophytic growths such as polyps and papillary erosions also speak against the cervix uteri as being *primarily* a glandular organ composed of tubular glands.

Summary

This study is based on the examination of 82 specimens of the cervix uteri, of which 15 were from premature babies from the twenty-sixth to the thirty-seventh week of gestation, 28 from newborn infants at term, and 39 from infants and children from the ages of 2 weeks to 14 years. The main conclusions were reached chiefly from the study of relatively thick microscopic sections cleared in xylol and oil of wintergreen.

The cervical canal in premature babies is characterized by a complicated system of longitudinal, transverse, and oblique folds of the mucosa and its underlying stroma.

The cervical mucosa of newborn babies at term presents a very marked secretory and proliferative activity of the lining epithelium. The folds previously noted become more pronounced and in addition there are numerous secondary outgrowths involving both the mucosal folds and the free surfaces of the canal.

Following birth, the cervical mucosa undergoes a regression from the stage of development attained in the newborn but the general configuration of multiple folds with secondary outgrowths persists at least until the age of 14 years.

There were no instances during this age period of well-defined tubular glands extending downward from the surface and branching irregularly in the manner of racemose glands.

My thanks are due to Dr. Alvin J. Cox, Jr., Professor of Pathology, for the autopsy material used in this study and for his assistance in developing the technique of preparing cleared specimens; to Miss Ann Krepelka for her technical assistance; and to Mr. Donald Longanecker and Mr. Paul Tracy for the photomicrographs.

References

1. Kölliker, A.: Manual of Human Histology, London, 1853, Sydenham Society.
2. Smith, W. Tyler: The Pathology and Treatment of Leucorrhea, Philadelphia, 1855, Blanchard and Lea.
3. Peaslee, E. R.: Human Histology, Philadelphia, 1857, Blanchard and Lea.
4. Satterthwaite, T. E.: A Manual of Histology, New York, 1881, William Wood & Company.
5. Pouchet, G., and Tourneux, F.: Précis d'Histologie Humaine, G. Masson, Paris, 1878.
6. Friedländer, C.: Physiologisch-anatomische Untersuchungen über den Uterus, Leipzig, 1870, Simmel & Co.
7. Nagel, W.: Arch. mikr. Anat. **37**: 620, 1891.
8. Meyer, R.: Arch. Gynäk. **91**: 579, 1910.
9. Hunter, R. H.: Contrib. Embryol. **22**: 91, 1930.
10. Scammon, R. E.: Proc. Soc. Exper. Biol. & Med. **23**: 687, 1925-1926.
11. Rosenthal, A. H., and Hellman, L. M.: Am. J. Obst. & Gynec. **64**: 260, 1952.
12. Novak, E.: Gynecological and Obstetrical Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company.
13. Stieve, H.: Ztschr. mikr-anat. Forsch. **11**: 291, 1927.
14. Fluhmann, C. F.: Am. J. Obst. & Gynec. **68**: 1447, 1954.
15. Hellman, L. M., Rosenthal, A. H., Kirstner, R. W., and Gordon, R.: Am. J. Obst. & Gynec. **67**: 899, 1954.
16. Fluhmann, C. F.: A. M. A. Arch. Path. **59**: 238, 1955.

Discussion

DR. JOHN L. McKELVEY, Minneapolis, Minn.—That large portion of the report which is descriptive microanatomy is not a subject for discussion since Dr. Fluhmann describes what he and the rest of us have seen. After he was so kind as to let me have a copy of his paper and the illustrations, 3 uteri were obtained and cut down. The first was from a 9-day-old child who died of congenital heart disease; this shows the late pregnancy and early postdelivery changes as Dr. Fluhmann has described them. The second was from a child of 7 months who died from biliary stricture, and the third from a 2½-year-old child who died from trauma. These show the regression of the folding in the endocervix and the decrease in size and function of the epithelial cells as they have been described.

The interpretation of the findings is another matter and discussion is justified. There seems to be every reason to believe that the rapid growth of the endocervix and the increased function of the gland cells is related to maternal endocrine sources either directly, indirectly, or both. There is no other acceptable explanation of the findings and particularly of the postnatal regression. On the other hand, one finds it difficult to use these findings to deny the essential racemose nature of the cervical glands. In the 9-day-old child, the epithelium at the bottom of the crypts or folds is formed into fingerlike projections like the branches of an inverted tree. The natural interpretation of this is that attempts are being made to form a characteristic racemose gland. This is not seen in the 7 months' specimen but begins to be seen again, although to a lesser degree, in the cervix from the 2½-year-old child. Further information of value might be obtained if one could gather for study a sufficient series to show the transitions in detail before, during, and after puberty.

Dr. Fluhmann has again mentioned in the full paper his concept of the origin of endocervical glands from the urogenital sinus. It is difficult to accept this. Studies of fetuses with gross deficiency of the urogenital sinus have shown normal findings in the endocervix and a primitive vaginal pouch lined by similar epithelium. Examination of the upper surfaces of vaginal septa which were once thought to be imperforate hymens shows similar

findings. And again, the endocervix is normal. A very occasional such specimen shows small areas of urogenital sinus epithelium in the upper vagina but not in the endocervix. These are inadequately explained but may be presumed to be the result of some invasion from the urogenital sinus which is not grossly evident.

DR. ARTHUR T. HERTIG, Boston, Mass.—In discussing this paper of Dr. Fluhmann's I point out one thing that perhaps most of you do not realize. He mentioned that he looked at 800 specimens and discarded 300 because they were not satisfactory. As a person who has spent a good deal of his adult life looking at sections and trying to interpret anatomic details upon which our profession, or at least our branch of the profession, is based, I should like to take this opportunity to say that Dr. Fluhmann has done a careful and painstaking job. He has looked at these sections himself and has done it from routine material. He has taken paraffin blocks, run them back to water, and sliced them in thick sections which he subsequently cleared. You have seen here some superb cleared sections which show a good many things in three dimensions.

It is perfectly clear that we do not quite know the answers to what the problem is, but he has shown us very clearly that what we have interpreted or what has been interpreted as glands are simply intervals or valleys between the rugae. It is a problem of whether the epithelium that forms the surface of these infoldings invades the stroma to form sulci or whether the stroma plus epithelium forms the ridges. What forms the sulci I am not sure, but at the bottom of these sulci, or valleys, or whatever you call them is the glandlike structure we are discussing at the moment.

I would like to show two of Dr. Fluhmann's slides again for my next comments (Figs. 5, *c*, and 1, *f*). Both are from cervices of the newborn. I had the privilege of seeing the original paper and I also had the privilege of seeing the original pictures. Moreover, I had the additional privilege of talking to Dr. Fluhmann today and going over some of the material with him.

In looking at this cleared section (Fig. 5, *c*), which is about 1 mm. in thickness, you will see these sulci, depressions, valleys, or whatever you choose to call them. In my opinion, this happens to be the most revealing slide he brought with him because one sees here in a single section the cut surface of the back of the block, the cut surface of the front of the block, and the bottom of these sulci. Moreover the bottom of many of the sulci are viewed tangentially so that the surface of the sulcus is easily visible. We see here these irregular clefts and crevices which are probably the mouths of the glandlike spaces—call them what you will—which are at the bottom of these sulci. When they are cut in a single thin section, they look much like the next slide (Fig. 1, *f*). You see the same crevices here with plicae and you see little epithelial rests, apparently separated from the bottom of the sulcus, which are interpreted as glands. I would suggest that probably the explanation of this problem is that there are sulci or gyri formed either by invasion of the epithelium or overgrowth of the plical stroma and epithelium together to form papilla-like structures. At the bottom of these sulci some secondary invaginations form. Again, we do not know whether it is by positive invasion of epithelium or overgrowth of the plical structures that this occurs but at this stage prior to puberty there is not seen the nice round gland opening but an irregular crevice which is merely a little, tiny valley within a valley.

I am quite in agreement with Dr. McKelvey that in the adult it would appear as though there were tubular or compound racemose glands, based on ordinary observations and serial section of cervices harboring carcinoma in situ. Probably there is a transition between the sort of thing Dr. Fluhmann has so painstakingly and so neatly shown and the racemose gland of the adult. A graduate student will help him this summer to investigate the problem in the adult cervix using serial sections with subsequent reconstruction. I think that they will thus throw some light on the nature of the glands in the mature cervix.

I am delighted to pay homage to a successful practicing clinician who is also a scholar of the anatomy of the female genital tract.

DR. KARL M. WILSON, Rochester, N. Y.—I may be digressing here a little bit but I cannot resist the temptation to point out that in spite of the fact that these very young

individuals have no truly formed glands, yet it is possible for an occasional one to develop malignant disease in the cervix. We have had 2 such examples on our service who were under 1 year of age. One of these died within a few days after admission, the diagnosis not being made until autopsy. The second, 11 months of age, came in with a story of a little bleeding. Fortunately she had a very intelligent mother who brought her in. With a nasal speculum a small amount of tissue was obtained which showed adenocarcinoma. Total hysterectomy was performed and that infant is now 8 years old and in excellent condition. It is true that there are not many of these cases, but in these very young individuals, in spite of an absence of typical glands, when malignant disease develops it is of the adenocarcinoma type. Whether a more mature type of gland develops before the malignant disease develops I do not know, but that is the type they show when malignant disease does develop.

DR. RONALD R. GREENE, Chicago, Ill.—Being from Chicago where everybody is an authority or a critic, I am having semantic troubles here as to what is a gland and what is a ruga, etc. You take a cross section and you may think you have wonderful glands but if you do it by another method it is a ruga or fold or plica. I do think Dr. Fluhmann's presentation would have been better if he had some serial reconstructions of these structures to show whether they were just folds or true glands.

Second, embryonically speaking, practically every gland develops as an outpouching of what was normal epithelium; whether it occurs in the embryo, at birth, 1 year post partum, or 10 years I do not think is relevant.

The third point concerns the response of the embryo to maternal hormones. Those are not maternal hormones. They are hormones produced in the placenta by fetal tissue.

DR. HERTIG.—I would like to comment on Dr. Wilson's discussion of the occurrence of cervical adenocarcinoma under the age of 1 year. It is well recognized both by the essayist and others that the cervix of the newborn and the child developing in utero shows changes which are quite like those of the mother's cervix, perhaps not to the same degree but of the same general type, even to having squamous metaplasia. It just happens that those adult patients during the intra- and postpartum periods have curious changes—and I have seen it only in the pregnant and postpartum cervix—that we call pseudoanaplasia, the endocervical glands showing pleomorphism and hyperchromatism. It could well be that the hormones associated with pregnancy do things to the cervix, fetal and maternal, which are physiologic but on occasion might be pathologic. I think this fits in with the general observations of Dr. Fluhmann and I am delighted to have Dr. Wilson bring up the matter because, as far as I know, nobody has adequately described this pleomorphism which occurs in the maternal cervix at or near term. It is my impression that the few adenocarcinomas of the cervix grow more rapidly and are more malignant in the pregnant than in the non-pregnant patient.

DR. FLUHMANN (Closing).—It was with some trepidation that I advanced evidence against our long-cherished belief that the cervix is composed of tubular glands, and it is very gratifying that these studies have met with such a sympathetic reception.

As Dr. McKelvey pointed out, the study of various congenital malformations speaks against the origin of endocervical epithelium from the urogenital sinus. The observation of Dr. Karl Wilson that carcinoma of the cervix in infants less than 1 year old is of an adenomatous nature also seems to favor a Müllerian beginning. Nevertheless, this question, first raised by S. Zuckerman, is still open and one cannot overlook the fact that this tissue in many ways behaves more like vaginal rather than endometrial mucosa.

The criticism advanced by Dr. Greene that this investigation was not based on serial sections is well taken and I intend to use this approach when continuing my studies of the adult cervix. However, I must emphasize that the photomicrographs of the thick cleared sections show tissues 100 times the thickness of conventional pathologic preparations. They are very convincing in demonstrating the folds and grooves and actually they should be considered as the equivalent of 100 serial sections. It is also quite correct that the hormones concerned are probably produced by the placenta, but nevertheless I do not hesitate to consider estrogen and progesterone as primarily maternal factors.

LONG-RANGE STUDIES OF THE BIOLOGIC BEHAVIOR OF THE HUMAN UTERINE CERVIX*†

II. Histology, Cytology, and Clinical Course of Cervical Disease

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THE precise interrelationships of inflammation, squamous metaplasia, atypical epithelial hyperplasia, carcinoma in situ, and invasive carcinoma of the uterine cervix still remain unsettled although there have been many studies in this direction.[2, 3, 6, 9, 12, 13, 17, 20, 23, 27] In 1938 Macfarlane[14, 15] set out to determine the value of semiannual pelvic examinations in the control of pelvic cancer in a group of volunteers. Her evaluation of this group was based upon clinical examination augmented by biopsy only when indicated by clinical findings. Thirteen hundred and nineteen women comprised her initial group; on the first examination carcinoma of the cervix was found in 3 women. Six hundred and sixty-six women continued in her study for an additional 13 years, but only one additional carcinoma of the cervix was discovered during that entire period. Throughout the course of the study 6 other carcinomas of the genital tract were diagnosed.

In a mass screening project, Erickson and associates[7] studied cervical disease in 108,136 women, employing a single vaginal smear taken by the patient's own physician or by trained technicians. No speculum or other instrumentation was used in this examination. They found by the use of this cytologic method alone that the vaginal smear was abnormal in 1.7 per cent of the total group. While simultaneous biopsy was not routinely taken, subsequent biopsy was advised in all women with suspicious smears. Among those who were subjected to biopsy, the prevalence of histologically proved cervical cancer on the first examination was 0.67 per cent, with an almost equal distribution between carcinoma in situ (0.36 per cent) and invasive cervical cancer (0.31 per cent).

Since the emphasis in cancer control is currently being and must always be placed upon diagnosis of the early lesion, we felt that extended study of the same cervices over a period of many years would permit not only the

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recognition of new cases of cancer itself but would also facilitate the assessment of possible "carcinoma precursors" as well. Thus, it was conceivable that changes destined to become malignant could be discovered before reaching the stage of what is now generally recognized as incontrovertible cancer. By following a geographically stable population at regular frequent intervals, it was considered possible to study the evolution of histologic and cytologic changes not only in the normal cervix but also in a broad group of clinically benign and malignant lesions of the cervix as well. If carcinoma of the cervix should develop in a given patient, it would be possible not only to section serially the entire cervix in which the carcinoma were found, but in addition all previously collected biopsy sections and cytology specimens could likewise be serially studied in retrospect, in order to assess the "precursor" patterns of carcinoma.

While the morphology of squamous metaplasia of the uterine cervix has been frequently reported and its implications widely discussed, a clear-cut relationship to atypical epithelial hyperplasia, carcinoma in situ, and invasive carcinoma has not been established. Much further study is necessary before definite conclusions may be reached. Similarly, the significance of epidermidization of cervical glands, a term not uniformly defined, requires additional study. A preliminary report of this phase of our work has already been published.[1] We have come to regard the cervical epithelial alterations variously described as atypical epithelial hyperplasia and carcinoma in situ as forming a spectrum of change merging one with the other. The evaluation of these histologic and cytologic differences is another important part of our study.

It appears that the whole question of the effect of environment, both immediate and remote, on cervical disease needs further exploration. The influence of such factors as age, parity, infection, laceration, and erosion as etiological agents in cervical neoplastic disease has been the subject of much speculation. One approach to obtaining answers for these questions lies in a longitudinal study designed to obtain further information as to the ultimate significance of any single one or combination of such factors. This aspect of the problem is presently being investigated and will form the subject matter of a future report.

The recent literature contains many reports of inquiries into the comparative relationships of cytologic and histologic findings in the human uterine cervix. However, we know of no previous concerted program wherein simultaneous clinical, cytologic, and histologic evaluations of the cervical changes in a large group of presumably healthy women have been carried out sequentially over a prolonged period of time. In embarking upon such a study, of which this is the first comprehensive report, it was our hope that by extending the clinical methods of Macfarlane and the cytologic approach of Erickson to include the comprehensive utilization of all available methods (clinical, cytologic, and histologic) many useful data could be obtained. It is our feeling that progress toward the goal of more accurate appraisal of the significance of these correlations lies in this direction.

Selection of Subjects

We feel that the manner in which our subjects were selected contributes to the significance of our work. The 954 women comprising the original study group were obtained from two sources. One group was composed of volunteers from the Seattle area, while the remaining patients were obtained from a large state mental institution. It was considered that the majority of each group represented a geographically stable population. Volunteers were obtained through word-of-mouth recruitment of women in the population at large who wished to have periodic gynecologic examinations as a part of the research project. This group comprised 211 women, or 22 per cent of the total group. Any woman with known carcinoma of the genital tract was excluded. Even though every effort was made to make the selection as random as possible, it is quite likely that some women with "cancerophobia" as well as those responding to cancer education programs were attracted to this study. It is to be emphasized, however, that these volunteers were not clinic or hospital patients nor were they currently under a physician's care for gynecologic disorders.

The hospital group comprised 78 per cent of the total. Here most of the selection factions mentioned above were probably not operative. As every new patient requiring long-term care for mental disease was admitted to the hospital, she was automatically included for repeated periodic study of the cervix. As in the volunteer group, only those already known to have cervical cancer were excluded. It is recognized that the disturbed mental status of the hospital group might influence the clinical recognition of cervical disease. While it was not always possible to obtain an adequate or reliable history from these patients, helpful information was often obtained from relatives, friends, and social service workers, as well as from hospital records. The mean and median age of the entire group was 42.6 years; the youngest patient was 14 years of age, the oldest 83 years.

The difficulties encountered in obtaining a group of "normal" subjects for a study such as this can be readily appreciated. It is recognized that if the results obtained are to be interpreted as representative of cervical disease in the general female population, then, from an epidemiologic standpoint, the selection of a truly representative study group is essential. In other words, the question as to whether the sample is an accurate reflection of the whole is pertinent. While the limitations of our group in this regard are fully appreciated, we feel that in general we are dealing with a much fairer sample of the population than has been the case in some other studies. In these reports, subjects have been selected almost invariably from among women attending clinics for gynecologic disease or from among hospitalized patients where numerous factors would be operative in preventing random sampling.

Method of Examination

All patients in both series were re-examined at intervals of six months throughout this study. At every visit, in addition to the clinical examination, evaluation included the simultaneous study of cervical cytology and histology. Although there was a rather high initial attrition as a result of patients' leaving the hospital or dropping out of the study for various reasons, the majority of the original group is still being followed. Some of those in the hospital series where follow-up was interrupted have returned and been reinstated.

At the time of the first examination all candidates were given a thorough clinical evaluation, including history, complete physical and gynecologic examination. At this time two smears were prepared, one from the cervical

canal and one from the vaginal pool of the posterior fornix. In the hospital patients, an Ayre spatula was used to obtain the cytologic material, while in the volunteer patients cotton applicators were employed. A punch biopsy was simultaneously obtained from the squamocolumnar junction or its immediate vicinity. On each subsequent examination these same procedures were again performed. Complete records were maintained on each visit including the precise location from which all material was removed. Biopsies were usually taken from the same part of the cervix unless specific lesions directed attention elsewhere.

In cases where either histologic or cytologic examination suggested cancer, the patient was admitted to the hospital for definitive evaluation, usually sharp conization of the cervix.

Diagnostic Standards

One of the most important features of any study dealing with the long-term follow-up of gynecologic disease is the use of uniform clinical, histologic, and cytologic diagnostic standards. From the inception of our project, the periodic examinations have been performed by a very small group of clinicians, all oriented in the same methods of examination and description, all using the same criteria for diagnosis, and all having a complete understanding of the background and purposes of the study. The volunteer patients have been seen throughout the study period by the same gynecologist, while the hospital group has been examined over the years by a group of four full-time members of the Department. It is believed that a high degree of uniformity in clinical interpretation from examination to examination has thus been assured.

All biopsy material has been reviewed and interpreted by a single pathologist. In order to assure the maintenance of even greater uniformity of description and diagnosis throughout the rather prolonged study period, each of the first 2,000 biopsies was subsequently re-evaluated by this same member of the team at a later period. Thus the criteria employed for designation of the various diagnostic categories have been applied as uniformly as possible throughout the entire study. It is felt that, while the specific diagnosis in some instances might well be questioned by others not utilizing our standards, at least uniform interpretation has been attempted by the same observer throughout the period of this project. All histologic diagnoses were made without any knowledge of the clinical or cytologic findings.

Likewise, all final cytologic evaluations were made by a single experienced cytologist. Here, too, the earlier material, which had originally been studied by several individuals, was subsequently reviewed and reclassified if necessary to assure maintenance of uniformity in interpretation. All cytologic interpretations were also recorded independent of any knowledge of the results of biopsy or of the clinical examination on the part of the cytologist.

Prospective Nature of Study

By studying a random group of "healthy" women in whom there was no known previous indication of cervical cancer, the changes found in the original and subsequent clinical, histologic, and cytologic examinations could be regarded as reflecting the prevalence and incidence of the diseases under consideration. This prospective approach seems more likely to reveal the epidemiology of disease than would the more commonly reported retrospective studies. The latter approach as a rule is concerned with the evaluation of

cervical changes in a group of "selected" patients, such as is found in a hospital or clinic group, who are known to have developed cancer. The forward-looking approach employed here is felt to eliminate or minimize the influence of selection factors inherent in the usual type of study, as well as to make available sequential histologic and cytologic material collected during the incipient stages of disease.

Prevalence and Incidence of Cervical Disease

In our consideration of the number of cases in each category, we have distinguished between prevalence and incidence. Prevalence is defined as the number of cases of any given type encountered in the initial study of a specified group. This figure, usually expressed in per cent, represents the total number of cases which have developed in the group up to the time of the study and which therefore are present in the group at the time of the first examination. Since many diseases persist for significant periods of time, the prevalence rate is cumulative and actually gives no information on the rate of development of new cases. This term has been confused with incidence, which is defined as the number of new cases of a given disease developing in a specific population within a definite period of time. Figures relating to incidence, then, actually represent the degree of risk of acquiring the disease in question incurred by a member of the group within a given period of time.

The results of the first clinical, histologic, and cytologic examinations reflect the prevalence of cervical disease in our group; that is, it is the total number of cases of each type present in the group at the time of this examination. The incidence of any of the changes under consideration may be derived by relating the number of new cases found in a given period to the total number of patients studied during this time. In so far as our group may be representative of the population at large, these figures may be extrapolated to give the prevalence and incidence of these diseases in this community.

Definition of Terms

Histologic.—

Cervix (normal cervix, cervicitis): The term "cervix" has been used to describe biopsies which include both normal ectocervical and endocervical elements. In other words, these biopsies showed both squamous and columnar epithelium. Biopsies containing only endocervical elements have also been included in this group. Varying degrees of inflammatory-cell infiltration of the stroma were so frequently encountered that no attempt was made to characterize these changes. They were so common in the region of the squamocolumnar junction where the biopsies were usually obtained as to be considered an almost "normal" finding. For this reason the term "cervicitis" was not coded to indicate abnormality, although a note was made of the more severe degrees of inflammatory change. The possible influence of this inflammation on the character of the adjacent epithelial elements was, of course, clearly recognized.

Ectocervix: This designation was used for biopsies in which there was only cervical stroma covered by mature squamous epithelium. No columnar cells were present either on the surface or within glands. Biopsies of this type were distinguished from those coded as "cervix" since they could not be clearly attributed to metaplasia and they could obviously not be considered capable of undergoing metaplasia. For this reason they were excluded from the total, as unsuitable biopsies, in calculating the prevalence and incidence of squamous metaplasia.

Metaplasia: The term "metaplasia" was selected to designate the changes variously referred to as epidermidization, epidermoidization, epidermidalization, etc.[2, 3, 13] We have defined squamous metaplasia as a benign condition in which surfaces normally composed of columnar epithelium become covered or replaced by an altered type of epithelial element akin to squamous cells. This change has been more fully discussed in our previous report[1] and is illustrated in Figs. 1 and 2. Although metaplasia involving the surface epithelium was routinely differentiated from that seen in glands, we have become convinced that such a distinction is of little significance since the epithelial changes in question are identical except as to location. Furthermore, repeated sectioning of this material showed that, in most cases, involvement of both surface and glandular epithelium could be demonstrated if a sufficiently detailed search were made. For these reasons we feel that metaplasia of surface or glandular epithelium should be regarded as a single entity.

Atypical hyperplasia: This term was adopted only because it seemed to be the simplest and most descriptive label for the changes observed. Many synonyms have been employed, including atypia, basal-cell hyperactivity, anaplasia, dissociated intraepithelial anaplasia, dysplasia, dyskaryosis, and dyskeratosis.[9, 17, 20, 25, 26] The large number of terms proposed to designate this change are only a reflection of its rather ill-defined nature and the general lack of agreement as to its significance. This diagnosis proved to be the most difficult to establish in our study. "Atypical hyperplasia," as we employed the term, refers to epithelial alterations which probably lie in a twilight zone between those changes which could be clearly recognized as inflammatory and those of a frankly neoplastic character (Figs. 3 and 4). In our work we have attempted to establish precise criteria for this diagnosis. These are in agreement with those recently employed by other authors.[9, 25, 26] Essentially, the changes under consideration are best described as a state of undifferentiation (or unripeness) of the cervical epithelium in which cells of a basal or immature type are carried out from their normal position toward the surface. There is, in other words, a loss of the normal maturation gradient in which basal cells give way gradually to more fully differentiated squamous elements. Since all degrees of this change are encountered, it is our feeling that these epithelial alterations are perhaps best regarded as forming a "spectrum" ranging from obviously benign changes at one end to frankly malignant alterations at the other end. A fundamental question in need of clarification has to do with the validity of the concept that, among the epithelial alterations in the cervix, squamous metaplasia may represent the lower end of the spectrum, while carcinoma in situ is found at the upper end, with all shades of "atypical hyperplasia" making up a broad middle ground. As already indicated, the evaluation of this concept is an important part of our study.

Carcinoma in situ: Some of the difficulties encountered in clearly defining the essential diagnostic features of carcinoma in situ of the cervix have already been touched on in the discussion of atypical hyperplasia. On the other hand, difficulties also arose in attempting to distinguish carcinoma in situ from invasive carcinoma. By the commonly accepted definition, the histologic changes in carcinoma in situ are regarded as identical to those of invasive carcinoma, save that the basal-cell layer in the former is intact, i.e., there is no invasion (Fig. 5).[3, 4, 6, 22, 23, 26, 27] Even when the uterus or at least the entire cervix is available for study, it is often difficult to exclude completely the presence of invasion since, at the minimum, serial block sections are required. Thus the difficulties which arise in attempting to reach a definitive diagnosis when only biopsy material is available are readily apparent. In fact, the final diagnosis of carcinoma in situ may well be questioned when based upon biopsy material alone.

Fig. 1.

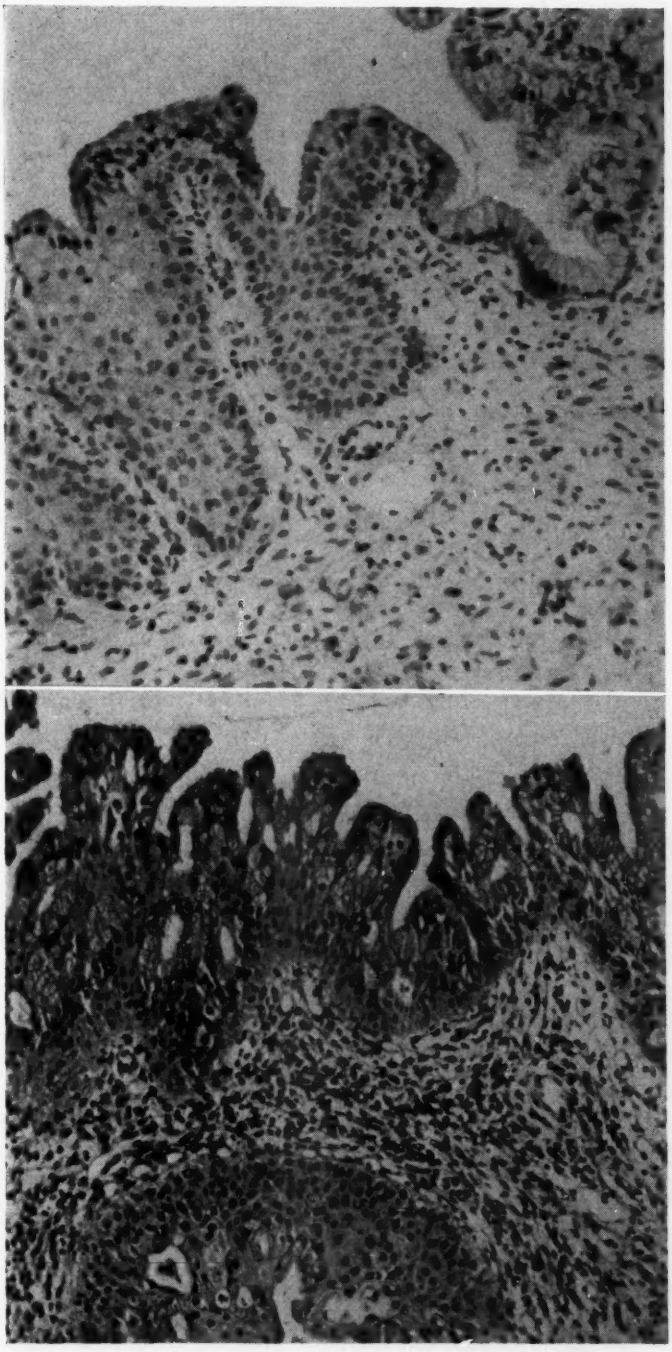


Fig. 2.

Fig. 1.—Surface metaplasia at junction showing continuation of partially flattened columnar cells over the squamous elements. (×325; reduced ¼.)

Fig. 2.—Squamous metaplasia involving surface and glandular epithelium. (×295; reduced ¼.)

It has been and still is our clinical practice, when epithelial alterations suggesting carcinoma in situ are encountered in a biopsy, to perform thorough sharp conization of the cervix in order to obtain adequate tissue for study. In the initial phase of this project, this same practice was followed. While conization might help to establish a final and unequivocal diagnosis of invasive or noninvasive carcinoma, it could at the same time possibly remove all of the lesion and thus preclude any further study of the natural history of the disease. Four patients with the diagnosis of carcinoma in situ underwent hysterectomy for their disease. It has been suggested that the tissue removed by the biopsy itself might encompass all of the neoplastic focus and hence result in failure to find similar or more severe changes on subsequent examinations.[3, 4, 13, 22] Examples have been reported in cases in which serial block survey of the entire cervix, excised immediately following biopsy diagnosis of carcinoma in situ, has failed to reveal any evidence of residual neoplastic changes in the removed specimen. It has also been held by some that the epithelial alterations regarded as carcinoma in situ or, at least, as being at the neoplastic end of the spectrum, are reversible, as in the cases associated with pregnancy.

Based upon experience gained so far in this study, a reasonable investigative approach to the problem appears to lie in the careful and prolonged follow-up of patients with biopsy changes interpreted as carcinoma in situ by combining meticulous physical, cytologic, and histologic evaluations at regular intervals. We have now adopted this plan of careful observation in this study group once the biopsy diagnosis of carcinoma in situ is made, and the regular follow-up period with repeat examinations has been reduced from every 6 months to every 3 months. Additional biopsies are, of course, frequently taken from multiple sites and serially sectioned. Patients with the established diagnosis of carcinoma in situ of the cervix have been dropped from the special study group and are being followed as a separate project.

Invasive carcinoma: The histologic diagnosis of invasive carcinoma of the cervix usually presented no problem. As indicated previously, however, the principal question of interpretation usually involved the distinction between carcinoma in situ and invasive carcinoma. It is to be emphasized that the fundamental decision here is whether the basement membrane has been penetrated. Because this point is so crucial, serial block, or better, serial sections of the cervical cone are necessary in every case where intraepithelial carcinoma is seen in the biopsy. This method of sectioning was employed in our study in every case where this question arose.

Cytologic.—

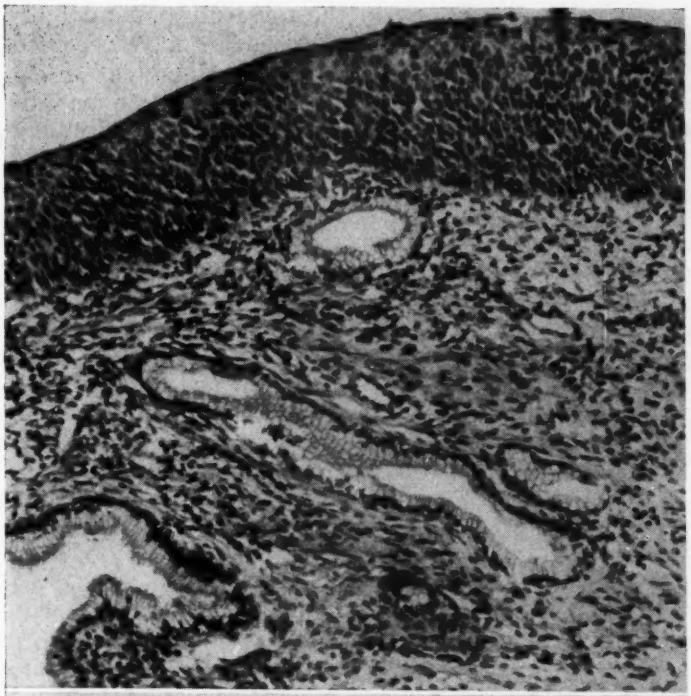
All smears were classified according to the criteria described by Papanicolaou.[18, 19] Only smears which were technically satisfactory were coded.

Class I Normal: These smears contained no atypical cells.

Class II Normal: These smears contained cells showing minor variations from normal. Such changes were generally associated with inflammatory lesions of the cervix, cervical erosion, Trichomonas vaginitis, and atrophic vaginitis. The cytologic atypia produced were usually easily recognized and quite distinct from those which would arouse a suspicion of malignancy. Since such smears could not be classified as strictly "normal," these cases were placed in the Class II category in order to separate them carefully from those showing atypical changes suggesting malignant progression.

Class III Suspicious: These smears contained cells which were regarded as suspicious of malignancy but not diagnostic. Although the cytologic criteria for malignancy are generally recognized and well defined, with individual

Fig. 3.



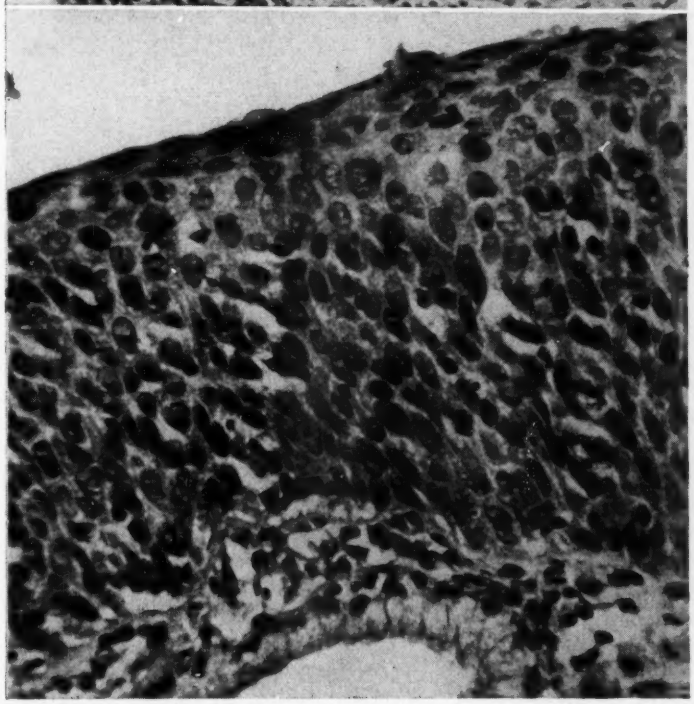


Fig. 4.

Fig. 3.—Atypical hyperplasia of the cervix in which cells of a basal type are carried from their normal basilar position toward the surface of the epithelium. (×190; reduced ¼.)

Fig. 4.—Atypical epithelial hyperplasia of the cervix, high power of Fig. 3. (×525; reduced ¼.)

interpretation, there is the inevitable case in which malignancy is strongly suspected but cannot be confirmed in the material at hand. The benign conditions which may produce such suspicious smears have received considerable attention in the literature.[26, 27] More definitive classification can often be attained with subsequent cytologic material on the same patient. While the Class III designation is the most difficult to interpret, it does indicate that the atypia noted extends beyond the limits generally seen in benign conditions. Such smears indicate the need for further evaluation of the patient.

Class IV Malignant: Smears placed in this class contained the cytologic changes seen in malignancy. The significant abnormalities were seen in the nucleus and consisted of enlargement of the nucleus, hyperchromatism, abnormal chromatin distribution, and anisonucleosis.

Class V Malignant: In smears where the described malignant changes were so pronounced as to preclude the absence of carcinoma, this designation was employed.

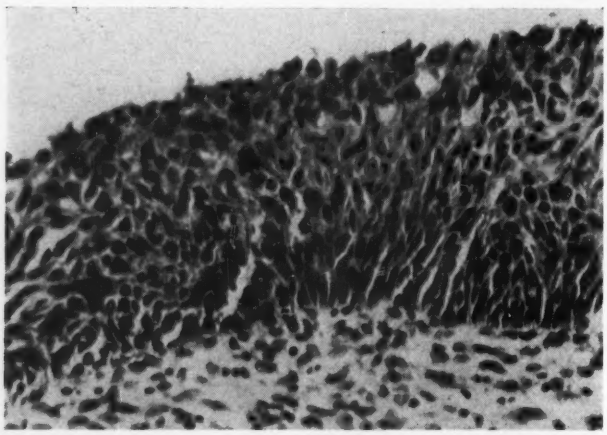


Fig. 5.—Carcinoma in situ of the cervix. Note the neoplastic elements throughout the entire thickness of the epithelium including the cells on the surface. The principal differentiating feature between the various degrees of atypical hyperplasia and of carcinoma in situ is the absence of neoplastic cells on the surface layer of the former and their presence in the latter. (×285; reduced ¼.)

Categorization of each smear according to Papanicolaou's classification led to confusion when attempts were made to compare the cytologic and histologic findings. It was therefore decided to abbreviate the cytologic classification without impairing accuracy in the interests of simplification of this report. All smears were grouped into three divisions: (A) the "normal" smear (Papanicolaou Classes I and II) where the cytologic interpretation indicated no definitely malignant process; (B) the "suspicious" smear (Papanicolaou Class III) containing definitely abnormal cells showing changes suggestive of malignancy but not permitting definitive interpretation; and (C) the "malignant" smear (Papanicolaou Classes IV and V), showing the characteristic malignant cell pattern.

Records

Because of the large volume and detailed nature of the information recorded on every patient at each examination, all data were coded and placed on IBM punch cards, thus permitting machine tabulation of all pertinent findings. This approach has made it possible to work out the various correlations which make up the subject matter of our reports. The data being

presented in the present report cover five examinations during the period, January, 1951, to November, 1954. Since the project is still in progress, data accumulated since 1954 are not yet available for presentation.

Results and Comment

Table I contains the parent data for this report. It is arranged to facilitate comparison of the cytologic and histologic findings of the first five semiannual examinations. It is thus possible to study the relationships of the over-all cytologic picture on the first examination to the over-all histologic pattern on the first as well as on all subsequent examinations. The relationships between the first histologic and subsequent cytologic examinations may also be evaluated. This method of comparison permits the introduction of time relationships into the study and emphasizes the nature of the cervical changes in the group as a whole.

The fact that the category of patients designated in the Table as "Others" has increased in number as the study has progressed requires explanation. In any examination where the histologic or cytologic material proved to be insufficient or was unsatisfactory due to artifactitious distortion or to other technical difficulties, the results were classified under "Others." Although there was seldom a problem in evaluating obviously benign or malignant tissue or cells in material of this type, the assessment of minor changes was often most difficult. All patients in whom a diagnosis of malignancy was established were dropped from the study and categorized as "Others" in subsequent follow-up. Patients in whom pelvic surgery was performed for noncervical lesions, but where removal of the cervix was necessary, were also subsequently listed in this manner. Although great care was exercised from the outset to select a geographically stable group for study, attrition did occur due to moving from the community or as a result of parole or discharge from the mental institution. Even though it has been impossible to examine completely some of the institutionalized patients at the prescribed time, they have been included in the subsequent compilations so that the number of patients still contained within the study group represents a significant percentage of the original population.

The diagnoses made on the satisfactory biopsies taken in the course of the first five examinations are shown in Table II. The decreasing number of patients seen in each subsequent examination reflects the patient loss at the time of that specific examination. The data on the patients available at the time of the fifth examination were considered adequate for satisfactory statistical evaluation.

As would be expected, most of the patients at each examination showed "normal" biopsies. In about 25 per cent of the biopsies squamous metaplasia of the surface or glandular epithelium could be demonstrated. It should be stressed here that this represents the frequency encountered in *all* biopsies. The "true" percentage of metaplasia can be computed only after exclusion of the biopsies containing ectocervix alone, since they were presumably taken from areas incapable of showing metaplasia. Although there was some variation in the relative number of cases showing normal tissue and metaplasia in the sequential examinations, these variations were small and probably not significant. There appeared to be a reciprocal relationship between the two diagnoses and together they comprised about 97 per cent of all cases studied.

Fourteen histologically proved carcinomas of the cervix were detected in the first three examinations during the first 12 months of the study period. Thirteen of these were detected during the first two examinations; the remaining case was diagnosed on the third examination. The latter, a carcinoma in

TABLE I. COMPARISON OF CYTOLOGIC-HISTOLOGIC DATA OBTAINED AT EACH OF THE FIRST FIVE EXAMINATIONS

	CYTOLOGY																								
	1ST EXAM					2ND EXAM					3RD EXAM					4TH EXAM					5TH EXAM				
HISTOLOGY	NORMAL	SUSPICIOUS	CA.	OTHER	TOTAL	NORMAL	SUSPICIOUS	CA.	OTHER	TOTAL	NORMAL	SUSPICIOUS	CA.	OTHER	TOTAL	NORMAL	SUSPICIOUS	CA.	OTHER	TOTAL	NORMAL	SUSPICIOUS	CA.	OTHER	TOTAL
1st Exam.—																									
Normal	521	8	4	23	556	360	4	2	190	556	323	8	2	223	556	293	9	1	253	556	234	16	3	303	556
Metaplasia	228	4	1	18	251	147	3	–	101	251	117	4	1	129	251	107	6	–	138	251	81	5	–	165	251
Atypical	19	6	1	2	28	11	4	1	12	28	9	1	2	16	28	7	2	1	18	28	9	2	1	16	28
Carcinoma	1	–	10	1	12	–	–	–	12	12	–	–	–	12	12	–	–	–	12	12	–	–	–	12	12
Others	96	1	–	10	107	62	–	–	45	107	48	1	–	58	107	41	–	–	66	107	29	3	–	75	107
Total	865	19	16	54	954	580	11	3	360	954	497	14	5	438	954	448	17	2	487	954	353	26	4	571	954
2nd Exam.—																									
Normal	402	9	–	21	432	388	4	1	39	432	342	7	2	81	432	317	8	2	105	432	251	18	2	161	432
Metaplasia	125	2	–	8	135	116	2	–	17	135	94	3	1	37	135	79	5	–	51	135	64	3	1	67	135
Atypical	11	1	2	–	14	8	3	–	3	14	6	1	1	6	14	6	2	–	6	14	7	1	–	6	14
Carcinoma	–	1	–	–	1	–	1	–	–	1	–	–	–	1	1	–	–	–	1	1	–	–	–	1	1
Others	327	6	14	25	372	68	1	2	201	372	55	3	1	313	372	46	2	–	324	372	31	4	1	336	372
Total	865	19	16	54	954	580	11	3	360	954	497	14	5	438	954	448	17	2	487	954	353	26	4	571	954
3rd Exam.—																									
Normal	365	3	1	19	388	344	4	–	40	388	354	11	1	22	388	329	11	–	48	388	255	18	1	114	388
Metaplasia	98	5	–	5	108	91	2	–	15	108	101	3	–	4	108	81	4	1	22	108	65	8	–	35	108
Atypical	5	1	–	–	6	2	1	1	2	6	4	–	1	1	6	3	–	–	3	6	3	–	1	2	6
Carcinoma	–	–	1	–	1	–	–	–	1	1	–	–	1	–	1	–	–	–	1	1	–	–	–	1	1
Others	397	10	14	30	451	143	4	2	302	451	38	–	2	411	451	35	2	1	413	451	30	–	2	419	451
Total	865	19	16	54	954	580	11	3	360	954	497	14	5	438	954	448	17	2	487	954	353	26	4	571	954
4th Exam.—																									
Normal	319	1	1	11	332	292	1	–	39	332	303	7	1	21	332	307	10	–	15	332	247	16	–	69	332
Metaplasia	110	3	–	8	121	108	2	–	11	121	115	1	1	4	121	110	5	–	6	121	82	7	1	31	121
Atypical	5	1	–	–	6	3	1	1	1	6	5	–	1	–	6	4	–	1	1	6	3	2	1	–	6
Carcinoma	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0
Others	431	14	15	35	495	177	7	2	309	495	74	6	2	413	495	27	2	1	465	495	21	1	2	471	495
Total	865	19	16	54	954	580	11	3	360	954	497	14	5	438	954	448	17	2	487	954	353	26	4	571	954
5th Exam.—																									
Normal	258	1	–	14	273	242	2	–	29	273	251	7	–	15	273	248	11	–	14	273	238	14	1	20	273
Metaplasia	107	3	–	4	114	97	1	–	16	114	105	2	1	6	114	105	4	–	5	114	94	6	–	14	114
Atypical	7	1	–	1	9	7	1	–	1	9	9	–	–	–	9	8	–	1	–	9	6	2	–	1	9
Carcinoma	2	1	–	–	3	1	–	2	–	3	1	–	2	–	3	1	–	1	1	3	–	1	2	–	3
Others	491	13	16	35	555	233	7	1	314	555	131	5	2	417	555	86	2	–	467	555	15	3	1	536	555
Total	865	19	16	54	954	580	11	3	360	954	497	14	5	438	954	448	17	2	487	954	353	26	4	571	954

situ, may well represent a lesion present at the beginning of the study. In this particular case, the three examinations were all carried out during the first six months since the initial smears showed malignancy and the first biopsy was atypical.

TABLE II. HISTOLOGIC DIAGNOSES BASED UPON SATISFACTORY TISSUE OBTAINED BY BIOPSY THROUGH FIVE EXAMINATIONS

EXAM.	NO. PATIENTS	NORMAL TISSUE		METAPLASIA		ATYPICAL		CARCINOMA	
		NO.	%	NO.	%	NO.	%	NO.	%
1st	847	556	65.6	251	29.6	28	3.3	12	1.4
2nd	582	432	74.1	135	23.2	14	2.4	1	0.2
3rd	503	388	77.1	108	21.5	6	1.2	1	0.2
4th	459	332	72.3	121	26.4	6	1.3	0	0.0
5th	399	273	68.4	114	28.6	9	2.3	3	0.8
Total	2,790	1,981		729		63		17	

Table III shows a similar analysis based upon the cytologic diagnoses of the satisfactory smears obtained during this same period. Approximately 96 per cent of all the vaginal smears were interpreted as normal. With subsequent examinations, the percentage of suspicious smears encountered showed a rather consistent rise. The significance of this trend can be evaluated only by reference to the development of neoplasia as shown by the continuing cytologic and histologic studies. Of all the smears, 3.0 per cent showed "suspicious" changes and 1.0 per cent were interpreted as malignant.

TABLE III. CYTOLOGIC INTERPRETATIONS BASED UPON SATISFACTORY SMEARS OBTAINED THROUGH FIVE EXAMINATIONS

EXAM.	NO. PATIENTS	NORMAL SMEAR (I, II)		SUSPICIOUS SMEAR (III)		MALIGNANT SMEAR (IV, V)	
		NO.	%	NO.	%	NO.	%
1st	900	865	96.1	19	2.0	16	1.8
2nd	594	580	97.6	11	1.8	3	0.5
3rd	516	497	96.1	14	2.7	5	1.0
4th	467	448	95.9	17	3.6	2	0.4
5th	383	353	92.2	26	6.8	4	1.0
Total	2,860	2,743		87		30	

TABLE IV. COMPARISON OF HISTOLOGIC FINDINGS WHERE SUSPICIOUS SMEARS WERE SIMULTANEOUSLY OBTAINED

BIOPSY DIAGNOSIS	SUSPICIOUS SMEARS		ALL PATIENTS (1ST EXAMINATION)	
	NO.	%	NO.	%
Normal	47	54	556	58
Metaplasia	20	23	251	27
Atypical	11	13	28	3
Carcinoma	2	2	12	1
Others	7	8	107	11
Total	87	100	954	100

The 87 "suspicious" smears found during the course of 2,860 patient examinations are compared with biopsy diagnoses reported on the same patients at the same examination in Table IV. The biopsy diagnoses and their relation to the total smears (first examination) are also given for comparison. The cytologic details noted in smears from patients with squamous metaplasia of the cervical epithelium were not found to differ significantly from normal. The incidence of squamous metaplasia among patients with suspicious smears

was no higher than among all patients. Thus it appears that the presence of metaplasia is not reflected by a smear suspicious of malignancy. Comparison of the biopsy pattern in the suspicious smear group with the biopsy findings of all patients at the first examination demonstrated a significant deviation (utilizing chi-square) in only one respect. Among the former, a disproportionately large number (13 per cent) showed atypical epithelial hyperplasia in the simultaneous biopsy when compared with the total group (3 per cent). This observation opens wide avenues of possible investigation, since atypical cellular patterns in cervical epithelium may frequently closely approach the changes of frank carcinoma and could even represent hitherto unrecognized precancer.

The thirty malignant smears encountered in the present study are shown in detail in Table V in order to facilitate correlation with the histology. Seventeen of these smears (57 per cent) were associated with primary cervical cancer. It is noteworthy that of the 30 smears 5 (17 per cent) were proved to reflect primary carcinoma of the ovary or fundus. Two of the patients with positive smears have been lost to follow-up; however, malignancy was not confirmed in either case in the simultaneous biopsy. Considerable effort has been made to establish contact with these patients but thus far this has been unsuccessful.

TABLE V. THE HISTOLOGIC FINDINGS WHERE CLASS IV AND V SMEARS WERE SIMULTANEOUSLY OBTAINED

EXAMINATION	CYTOLOGY (NO. OF PATIENTS WITH MALIGNANT SMEARS)	HISTOLOGY (CARCINOMA)			FALSE POSITIVE	LOST TO FOLLOW-UP
		CERVIX	FUNDUS	OVARY		
1st	16	11		2	1	2
2nd	3	2		1		
3rd	5	3	1		1	
4th	2	1			1	
5th	4		1		3(?)	
Total	30	17	2	3	6	2

We subscribe to the view that the vaginal smear and the cervical biopsy should not be regarded as opposing methods of diagnosis, but rather as complementary instruments in cancer detection. One of the principal advantages of studies such as this is the opportunity provided for the assessment of the relative accuracy of the various methods used in diagnosis of early cancer. The reliability of the vaginal smear in the detection of cervical cancer has been reported as showing wide variation. This may be partly explained by the differences in criteria established by various investigators. Nesbitt and Brack,[16] in reviewing the data reported by fifteen separate investigators, found the accuracy of cytologic diagnosis in cervical cancer to vary from 70 to 100 per cent. The evaluation of a false positive or a false negative smear may be most accurately made on the basis of simultaneous tissue studies combined with careful follow-up unless the entire cervix is available for serial sectioning. A single examination with simultaneous smear and biopsy, without subsequent study, offers a hazardous basis for assuming that one or the other or both are negative since the error of either method may vary from 5 to 30 per cent. In this respect, we feel that the results of our study have a validity not present in some reports, since all but 2 of our patients who had either positive smears or biopsies are being followed at the present time.

The figure for false positive smears is derived by relating the number of smears which were erroneously diagnosed as malignant (where careful study

by all other means as well as adequate follow-up failed to confirm the presence of malignancy) to the total number of true negative smears. Although most observers have reported false positive results in up to 4 per cent of cases, Graham and Meigs[11] have reported the excellent figure of 0.04 per cent obtained at the Massachusetts General Hospital in 1949. We found a total of 6 false positive smears (0.2 per cent of 2,830 true negative smears, Table V). Several individual cases deserve further comment. In one case where a false positive smear was recorded in the fourth examination, subsequent serial biopsies from the cervix showed markedly atypical epithelial changes. In view of the many recent reports suggesting that pronounced basal-cell hyperactivity may precede the development of carcinoma in situ, this patient's course is being followed, untreated, with particular interest. Similarly, in the 3 patients who apparently showed false positive smears on the fifth examination, the demonstrated frequency with which cytologic changes have indicated malignancy before confirmation by random biopsy makes it hazardous to conclude finally at this early date that these are true false positive diagnoses. While we recognize that careful total studies of amputated or coned cervical tissue from these patients might at once clarify the issue, it would, at the same time, be undesirable since it would render the patient unsuitable for continuation in this project which was specifically designed to explore the progressive development of cervical lesions.

Fourteen of the 17 cases of carcinoma of the cervix in our study were correctly diagnosed by cytology, an accuracy of 82.4 per cent, with 17.6 per cent false negative smears (Table VI). Graham and Meigs reported 10 per cent false negative smears, while other reports have listed figures from 0 to 30 per cent. Of our 3 false negative smears, 2 were suspicious and only one was described as being normal. Although the smears did not show malignancy, evidence of cancer was found in the simultaneous histologic preparation. Two of these were invasive carcinomas, while the third was regarded as carcinoma in situ on biopsy. While many investigators[16] have classified the "suspicious" smear obtained from patients with histologically proved cancer as a "malignant" smear in the calculation of their results, we feel that unless the smear was definitely interpreted as "malignant" it should be considered as a false negative. The "suspicious" smear, in our analysis (Table IV), does not carry with it the implication of malignancy, since, when patients with suspicious smears are studied as a group, the frequency of histologically demonstrable malignancy within that group is probably not significantly higher than in the total number of patients. Therefore, it should be emphasized that if cancer is shown to be present on histologic examination, a simultaneous "suspicious" smear must be considered as a false negative smear. Patient No. 716 is particularly interesting in that the initial histologic and cytologic findings were normal, and changes consistent with malignancy developed during the observation period only after three normal smears and four negative biopsies.

It is interesting to note in this connection that the figure for false negative biopsies, where *single* biopsies of the cervix are obtained, is usually about 30 per cent, suggesting the greater reliability of cytology as a screening method in the diagnosis of malignancy. This rate of false negative biopsies has not been confirmed in our experience, however. With reference again to the correlation of cytologic and histologic patterns in the cases of cancer encountered in our study (Table VI), 4 false negative biopsies may be assumed to have occurred in 3 patients (the first and second in Patient No. 50, the fourth in Patient No. 601, and the second in Patient No. 635). Unsatisfactory smears or biopsies were not considered in determining the accuracy of a given method. Among the 21 satisfactory biopsies taken in these 17 patients at a

time when malignancy was presumed to be present, 19 per cent must be considered as false negative. Therefore, in our hands, the use of the vaginal smear alone or of the single cervical biopsy alone, in the diagnostic screening for cervical cancer, appeared to offer approximately equal accuracy.

TABLE VI. ILLUSTRATION OF THE SIMULTANEOUS AND ANTECEDENT CYTOLOGY IN PATIENTS WHO PRESENTED HISTOLOGICALLY PROVED MALIGNANCY AT ANY TIME DURING THE ENTIRE STUDY

	HISTOLOGY					CYTOLOGY				
NO.	1ST	2ND	3RD	4TH	5TH	1ST	2ND	3RD	4TH	5TH
33	In situ					Malig-nant				
50	Atypi-cal*	Atypi-cal*	In situ			Malig-nant	Unsat-isfac-tory	Malig-nant		
53	Inva-sive					Malig-nant				
102	In situ					Malig-nant				
125	Inva-sive					Malig-nant				
286	Normal	Inva-sive				Suspi-cious	Suspi-cious*			
334	Inva-sive					Malig-nant				
347	Inva-sive					Malig-nant				
439	Inva-sive					Malig-nant				
601	Atypi-cal	Unsat-isfac-tory	Unsat-isfac-tory	Atypi-cal*	Inva-sive	Suspi-cious	Malig-nant	Malig-nant	Unsat-isfac-tory	Malig-nant
635	Normal	Nor-mal*	Unsat-isfac-tory	Unsat-isfac-tory	Inva-sive	Suspi-cious	Malig-nant	Malig-nant	Unsat-isfac-tory	Malig-nant
651	In situ					Malig-nant				
662	Inva-sive					Malig-nant				
667	In situ					Malig-nant				
670	Inva-sive					Nor-mal*				
716	Normal	Normal	Normal	Normal	In situ	Normal	Normal	Normal	Suspi-cious	Suspi-cious*
954	Inva-sive					Malig-nant				
Total with cancer	12	1	1	0	3					
Total	17 cases, 11 invasive 6 in situ									

*False negative.

Carcinoma of the cervix, in situ or invasive, was detected by biopsy in 12 of these 17 patients on the first examination. Of the remaining 5 patients in whom cervical carcinoma was later proved histologically, 3 had suspicious smears on the first examination and one a malignant smear. It will be seen that the patient with the malignant smear (No. 50) did have atypical changes in the biopsy obtained at the time. One might be inclined to presume that the 3 patients with suspicious smears (Nos. 286, 601, 635) actually had carcinoma on the basis of cytologic findings alone. It might be argued, however, that the suspicious smears reflected only atypical epithelial changes in

the cervix, which subsequently evolved to the stage of malignancy. The suspicious smear has indeed been shown in our study to reflect such atypical changes, and the intervals of 17 and 20 months that elapsed before the final histologic evidence of malignancy in 2 of these patients lends credence to this view.

Determination of the precise time of onset of a disease presents a real problem in the analysis of a series of cases in so far as prevalence and incidence are concerned. In our study we have resolved this problem by presuming the presence of carcinoma in our patients from the time the first clinical, histologic, or cytologic examination indicated the presence of malignancy, provided this was subsequently proved by biopsy. We would emphasize that this is a retrospective solution, possible only because of simultaneous acquisition of the material. It must also be strongly emphasized that in clinical practice the malignant smear alone is not sufficient basis for the definitive diagnosis of cancer and that in our opinion no patient should be treated for gynecologic malignancy without definite histologic confirmation. On the basis of these criteria, we feel that the 13 cases of malignant cervical changes in the biopsy or in the smear at the time of the first examination, where the positive smear was subsequently confirmed by biopsy (No. 50), represent the prevalence of carcinoma in this group. By relating these 13 patients to the total of 847 patients who had satisfactory biopsies and smears, the prevalence of cervical cancer among our patients was found to be 1.54 per cent. Five of these were in situ carcinomas, a prevalence of 0.59 per cent; and 8 were invasive, a prevalence of 0.95 per cent. Four more carcinomas of the cervix, 3 of them invasive and one in situ, have been proved histologically throughout the remainder of the present study period. If we assume that these are "new" cases which have developed after the inception of the study, which we have arbitrarily defined as embracing the first three examinations, and relate them to the total of 399 patients followed at each one of the five examinations, we may tentatively conclude that the incidence of cervical carcinoma in our group is about 0.5 per cent per year. The number of cases involved and the follow-up period so far are, of course, both too small to permit final statistical evaluation. The tentative findings, however, do suggest the degree of risk of developing carcinoma of the cervix to which the members of this population group are exposed.

Summary and Conclusions

1. The initial appraisal of a prospective long-term study of the clinical, histologic, and cytologic alterations encountered in the cervical epithelium of 954 presumably healthy women examined at 6-month intervals is presented, with emphasis upon the unique features of the background, scope, objectives, and methodology of the study.

2. An attempt has been made to employ consistent techniques of clinical, histologic, and cytologic examination and description of findings, as well as uniformity in definition of terms and diagnostic standards. With such consistency and uniformity, comparisons of results within the same study and with the results of other studies become more meaningful.

3. The epidemiologic approach employed in our study permits a satisfactory analysis of special problems related to unbiased selection of subjects and to prevalence and incidence of malignant and other cervical disease.

4. Interrelationships of histologic and cytologic findings in simultaneous examinations of the same cervix are explored and the results tabulated and discussed.

5. Squamous metaplasia of surface or glandular epithelium of the cervix was present in 25 per cent of all biopsies; the problem of squamous metaplasia is reviewed in relation to cervical neoplasia.

6. The "suspicious" smear deserves special attention. Each suspicious smear was studied in relation to the histologic findings in the simultaneous biopsy. The suspicious smear does not indicate malignancy and must be regarded as a "false negative" if the simultaneous biopsy is positive.

7. Sixteen per cent of the positive smears reflected malignancy arising in the uterine fundus or ovary.

8. The false positive smear rate was 0.2 per cent.

9. The false negative smear rate was 17.6 per cent.

10. Among the patients in our study known to have carcinoma, the single cervical biopsy failed to reveal the presence of cancer (false negative biopsy) in 14.3 per cent.

11. At the first examination, cancer of the cervix was diagnosed histologically in 12 patients.

12. Although the difficulty of determining the precise time of onset of a disease which presumably develops gradually over a period of time is recognized, evidence of cervical cancer present at the first examination, on the basis of the combined histologic and cytologic findings, indicated a prevalence rate of 1.5 per cent in our group.

13. The incidence of the development of carcinoma of the cervix was 0.5 per cent per year in our group of patients.

14. In our experience the vaginal smear and the single cervical biopsy appear to offer approximately equal accuracy in diagnostic *screening* for cervical cancer.

15. A high degree of accuracy in the detection of cervical disease and other gynecologic malignancy is possible on the first examination when the complete gynecologic survey includes visualization of the cervix, study of cytologic material not only from the vagina but also from the cervical canal, and study of biopsy material simultaneously removed from the squamocolumnar junction of the cervix.

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References

1. Brown, David V., and de Alvarez, Russell R.: Schweiz. Ztschr. Path. u. Bakt. 18: 781, 1955.
2. Carmichael, R., and Jeaffreson, B. L.: J. Path. & Bact. 49: 63, 1939.
3. Carson, Robert, and Gall, Edward: Am. J. Path. 30: 15, 1954.
4. Carter, Bayard, et al.: AM. J. OBST. & GYNEC. 71: 634, 1956.
5. Daro, August F., Rubenstein, William, and Gollin, Harvey: AM. J. OBST. & GYNEC. 65: 364, 1953.
6. Dunn, John E., Jr.: Cancer 6: 873, 1953.

7. Erickson, C. C., et al.: J. A. M. A. **162**: 167, 1956.
8. Foote, F. W., Jr., and Stewart, F. W: Cancer **1**: 431, 1948.
9. Galvin, G. A., Jones, H. W., and Te Linde, R. W.: AM. J. OBST. & GYNEC. **70**: 808, 1955.
10. Gordon, John E., Snegireff, Leonid S., and Taylor, Ruth S.: Am. J. M. Sc. **229**: 317, 1955.
11. Graham, Ruth M., and Meigs, Joe V.: AM. J. OBST. & GYNEC. **58**: 843, 1949.
12. Grand, C. C., and Ayre, J. E.: Obst. & Gynec. **4**: 411, 1954.
13. Howard, L., Jr., Erickson, C. C., and Stoddard, L. D.: Cancer **4**: 1210, 1951.
14. Macfarlane, Catharine, Sturgis, Margaret C., and Fetterman, Faith S.: AM. J. OBST. & GYNEC. **62**: 102, 1951.
15. Macfarlane, Catharine, Sturgis, Margaret C., and Fetterman, Faith S.: AM. J. OBST. & GYNEC. **69**: 294, 1955.
16. Nesbitt, R. E., and Brack, C. B.: AM. J. OBST. & GYNEC. **68**: 761, 1956.
17. Nesbitt, R. E.: Obst. & Gynec. **6**: 239, 1955.
18. Papanicolaou, G. N.: Am. J. Clin. Path. **19**: 301, 1949.
19. Papanicolaou, G. N., and Traut, H. F.: Diagnosis of Uterine Cancer by the Vaginal Smear, New York, 1943, The Commonwealth Fund.
20. Peckham, Ben, Greene, R. R., Chung, J. T., Bayly, M. A., and Benaron, H. B. W.: Surg., Gynec. & Obst. **99**: 401, 1954.
21. Peckham, Ben, et al.: AM. J. OBST. & GYNEC. **67**: 21, 1954.
22. Pund, E. R., and Auerback, S. H.: J. A. M. A. **131**: 960, 1946.
23. Pund, E. R., Nettles, J. B., Dick, F., Jr., and Cardwell, E. S., Jr.: South. M. J. **41**: 711, 1948.
24. Reagan, James W.: Am. J. Clin. Path. **22**: 231, 1952.
25. Reagan, James W., Hicks, Dorothy J., and Scott, Roger B.: Cancer **8**: 42, 1955.
26. Reagan, James W., Seidemann, Ilse L., and Saracusa, Yolanda: Cancer **6**: 224, 1953.
27. Reagan, James W., and Hicks, Dorothy J.: Cancer **6**: 1200, 1953.

Discussion

DR. DAVID N. DANFORTH, Evanston, Ill.—I wish first to present my experience with a group of private patients who were seen in my office over the past 8 years and whom I believe to be as a group generally comparable to those presented by the essayist. Most of these patients came into the office for routine periodic examination. Many were referred because of the finding of a cervical lesion by the referring physician on routine examination. Some had complaints of abnormal bleeding or discharge. The findings can be summarized in tabular form:

1. Vaginal Smears			
Total smears	2,566		
Grade III	72		2.8%
Negative in follow-up		67	
Grade IV in follow-up		5	
Grade IV	19		0.7%
Carcinoma in situ		14	
Invasive carcinoma		5	
2. Pathologic Diagnosis, 409 Cervical Biopsies			
Chronic cervicitis	237		57.9%
Squamous metaplasia	109		26.6%
Basal-cell hyperplasia	29		7.1%
Carcinoma in situ	17		4.1%
Invasive carcinoma	9		2.2%
Other	13		3.2%
3. Basal-Cell Hyperplasia, 29 Cases			
Lesion absent in follow-up biopsies	15		
Lesion persisted without change	12		
Carcinoma in follow-up biopsies	0		
Lost to follow-up	2		
4. Carcinoma in Situ, 17 Biopsy Diagnoses			
Vaginal smear also positive	13		
Vaginal smear Grade III	4		
Conization specimen			
Lesion shown to be preinvasive	14		
Lesion shown to be invasive	1		
No lesion whatever	2		

For biopsy purposes the Gaylor punch was used in localized lesions. In the case of a Grade III or IV smear in which no gross lesion was evident, the Gusberg instrument was used to remove the entire squamocolumnar junction for study. Extensive and uniformly circumoral lesions were often either biopsied in toto with the use of the Gusberg instrument or four-quadrant biopsies were obtained with the Gaylor punch. In cases showing preinvasive carcinoma in the biopsies or in those with malignant smears in which the biopsies showed no cancer, sharp conization was done under anesthesia and serial blocks prepared. I believe this approach is in agreement with that which is clinically recommended by Dr. de Alvarez. His results demonstrate clearly that in cancer detection the first examination is the most important, since 12 of the total number of cancers were diagnosed at this visit. In one of the remaining 5, actual malignant cells were present at the first visit but the lesion was not diagnosed until the third. In 2, the smear showed malignant cells at the second visit, but no lesion was found until the fifth visit. It is reasonable to presume that in these 3 cases, delay in diagnosis was due merely to the fact that the biopsy was taken from an unaffected portion of the cervix and that in any event the lesion, which was ultimately found, was probably quite different from the one which produced the first positive smear.

No mention is made of the presence or absence of a gross lesion nor of the location of the lesion in the in situ carcinomas, which would be very informative. With reference to in situ carcinoma, so-called false positive smears may be due to the occurrence of the lesion high in the cervical canal. In one of my own cases where the smear was positive and all four of the four-quadrant biopsies were negative, the lesion was found to be present at the topmost portion of the excised cone.

Dr. de Alvarez' appraisal of this extensive material was hampered, and I believe weakened, by his desire to maintain an intact cervix for future study. Since carcinoma in situ is frequently a focal lesion, a single punch biopsy as employed in this study may on the one hand remove the lesion completely or may, on the other, disregard entirely a well-developed lesion in another part of the cervix. Thus, to clarify the issues raised by this paper, I should think it necessary to have serial block sections of each cervix in which the smear was either suspicious or positive and in which bopsies were negative for invasive carcinoma. By this means only could one determine with certainty the cervical changes concerned in the production of the Grade III smear. Also, it is probable that most if not all of the so-called false positives would be eliminated by this serial study. Although it is correct that patients subjected to this complete study would be eliminated from any future consideration, nevertheless it does seem evident that by no other means can the stated purposes of this paper be answered.

DR. EMIL G. HOLMSTROM, Salt Lake City, Utah.—Dr. de Alvarez' "prospective" approach to the problem has long been recognized as an essential one. Further results of their studies will be awaited with interest by all of us.

I am pleased to note that the classification of smears into the three categories of normal, suspicious, and positive has been adopted instead of an attempt to subdivide these further into the five Papanicolaou categories. The smear is being more and more widely utilized as a screening procedure, not only by members of our specialty but by all practitioners. The simpler the reporting can be made, the more likely it is that the indicated follow-up procedure will be carried out.

This has been presented as a preliminary report but, for me, some of the findings to date are of considerable interest. For example, it is reassuring to me that supporting evidence has been found for some beliefs which I had previously held on the basis of training and clinical impression alone. I refer particularly to the concept that the presence of metaplasia or epidermidization in the cervix is *not* associated with a higher incidence of, or susceptibility to, carcinoma. Vaginal smears obtained from women who showed metaplasia of the cervix in simultaneously obtained biopsies showed no essential differences from the smears obtained from women with normal cervices. Conversely, biopsies taken from women with "suspicious" smears showed no higher incidence of metaplasia.

One aspect of the report raises a question in my mind. Of the 30 positive smears discovered to date, 6 are regarded as false positives. Even though these represent a very small percentage of the total (0.2 per cent), I do not feel that they should be called false positive. Perhaps it would be more proper to call them unproved positives. In order to carry his study to completion, Dr. de Alvarez has deliberately not subjected these patients to a complete, searching examination. It is likely that eventually all these patients will show evidence of a carcinoma somewhere. Cells interpreted as carcinoma have been found in the smears obtained from these patients and it is the physician's responsibility to find where these cells are coming from.

We have had an opportunity to study a smaller but similar group of women by smears alone. The first 400 asymptomatic women turned up four positive smears, a prevalence rate similar to that reported by Dr. de Alvarez. Inasmuch as time did not permit the presentation of any of Dr. de Alvarez' cases, I would like to take two minutes to present 2 of ours.

The first is an asymptomatic 41-year-old Jewish woman. Her smear was positive. Her cervix was normal except for a small Nabothian cyst anteriorly. The conization biopsy showed only one area, almost at the upper edge of the cone, which was interpreted as intraepithelial carcinoma with glandular extension. The hysterectomy specimen showed no evidence of residual carcinoma.

The second patient is a 40-year-old nullipara who had been subjected to bilateral salpingo-oophorectomy at the age of 20 for pelvic inflammatory disease. (An interesting sidelight is that at no time did she develop vasomotor symptoms despite the early castration.) Her smear showed large clumps of malignant cells. The cervix was very atrophic and completely epithelized. The cone showed an intraepithelial carcinoma with glandular extension. The hysterectomy specimen again showed no carcinoma.

Cases of this sort are now being encountered frequently by all of us. We assume that by uncovering them in the asymptomatic stage we are decreasing the incidence of invasive carcinoma and I have a feeling that we are. But is this necessarily so? Only long-range studies carried out over many years and involving many thousands of patients will provide the answer. The time has come for a pooling of experience. This has been suggested many times by various groups interested in the problem. To my knowledge this has never progressed beyond the discussion stage. I suggest that Dr. de Alvarez, with the excellent start which he has outlined here, proceed at once to implement such a collaborative study.

DR. RONALD R. GREENE, Chicago, Ill.—In general our findings agree very well with those of the essayist. There is only one point I want to emphasize. There have been very few series in the literature in which routine biopsies and smears have been done at the same time in which the findings between smears and biopsies have been correlated. We have conducted a similar study, including only cases subjected to four-quadrant biopsies and Papanicolaou smear the same day, same time, same sitting. We had thought we were pretty good as cytologists but actually, in a series of about 750 patients, weighted by many, many Negro patients so that we have almost 50 carcinomas in that group, the accuracy of our interpretation of the smears only ran 86 per cent. We have 14 per cent false negative. I think in most series, if we just compare the smears in patients in whom there is proved carcinoma, it will not run to the 96 per cent that is claimed. The smear is a beautiful tool. It is indeed a wonderful tool but it is not invariably accurate, and I think we should all keep that in mind.

One other point. I do not think Dr. Danforth's figures are comparable to Dr. de Alvarez' because his are private patients and I believe the data in the literature show a lower rate of carcinoma in private patients than in public institutions, particularly if they are weighted by many Negro patients.

DR. ROGER B. SCOTT, Cleveland, Ohio.—Many years ago it seemed ridiculous to believe that studies of stained cells from the cervix would be of much value, particularly

since there was still much confusion in the exact diagnosis from a full tissue section. Since then I have had the good fortune to work with a topnotch cytologist and have changed my mind. I wish to question the essayist's remark that he regards a suspicious smear as negative, if he finds no lesion on biopsies. A properly taken cellular study by aspiration of the endocervical canal and scraping of the portio, properly fixed and read by a competent cytologist, represents an excellent comprehensive sample of the cervix. It is unfortunate that during the developmental stage of clinical cytology a paper was published which reported that 30 per cent of the overt invasive cancers of the cervix showed negative cytology. Just visualize these infected, necrotic lesions—one could hardly expect to get a good cellular sample from even 70 per cent. A cellular study from a cervix with no overt lesion is quite different. When my cytologist, who is also an excellent pathologist, finds suspicious or malignant cells, it is up to me to locate the source of this exfoliation. I realize that the essayist has his problems. He does not want to ruin his controls and his histologic studies are only by punch biopsy. The lesion might be higher in the cervical canal. Until all the tissue is available for study, an accurate histologic study cannot be made.

I wish to mention one unusual experience, in which a carcinoma of the gall bladder was first suspected by cytology studies from the cervix. Malignant cells were reported, so a curettage and thorough biopsies were done prior to laparotomy for large myomas. These sections were benign. At laparotomy the patient had myomas and also abdominal carcinomatosis, originating in the gall bladder. After spending about $70 on semiserial studies of the uterus, a secondary focus of adenocarcinoma was found in the endometrium. Of course this is a rather ridiculous example, but it does represent the spot I am in when the cytologist reports "malignant cells." It is up to me somehow to find the lesion.

DR. DE ALVAREZ (Closing).—The results of this study were so intriguing at the end of the first 3 years that, even though the initial financial support had expired, we felt that we had learned much and that by carrying this on as a prospective study there was much more to learn. I have considered the possibility of a collaborative study and brought this to the attention of one group but the economic difficulties eclipsed our enthusiasm.

There are three points that have been brought out by the discussers which I think deserve emphasis. While we do not recommend this *single* cervical biopsy approach to rule out significant cervical disease, we were interested in determining the reliability of a single cervical biopsy. The false negative biopsy rate in our group was 14 per cent. However, even when four-quadrant biopsies are taken, one is not assured of 100 per cent positive results where carcinoma is present. The majority of studies dealing with this aspect report a false negative incidence of 10 per cent.

Second, the so-called false positive smear if persistent—and here I agree wholeheartedly with what Dr. Holmstrom and Dr. Scott have said—must be regarded as reflecting malignancy at some location in the pelvis. Whether it originated from the pelvis or not, its presence in the pelvis could permit transmission to the cytologic preparation. We have detected carcinoma of the stomach by vaginal cytologic means. I agree with Dr. Holmstrom that "false positive" is not the most accurate terminology and would suggest that such smears be called "conditional positives"—conditioned by the fact that we must prove that there is some reason for the positivity. In the clinical practice of our specialty, there should be no debate that exhaustive studies must be carried out, even to the degree that essential reproductive structures be removed, to implement such investigations. While no one can justify deliberate continuation of a known pathologic process to the point of incurability, it may be professionally appropriate and philosophically sound to explore the possible gradations and transcendence from normal tissue and varying degrees of benign cervical processes to stages that we know as cervical malignancy, under closely scrutinized research conditions.

The question was asked by Dr. Danforth about clinical inspection of the cervix. As you recall, others found 4 carcinomas in 13 years by clinical inspection. One cannot rely

upon clinical inspection alone or clinical suspicion. We did go back over our material, our clinical impressions during examination, and coded them on IBM cards and found that on the first examination 17 patients had clinical "malignancy" as we looked at and felt the cervix, yet only 4 had actual confirmed histologic malignancy. The other 8 carcinomas of the cervix found by us on first biopsy were in the type of cervix Dr. Holmstrom showed—clinically normal.

I think a single cervical biopsy is not the best screening method. Neither do I consider a single cervical smear as the best method for screening gynecologic cancer. If we are to screen and expect the best results, the combination of simultaneous smears and biopsy should be taken.

THERAPY OF CARCINOMA IN SITU*

Implications From a Study of Its Life History

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IN ORDER to treat a disease properly it is necessary to be thoroughly familiar with its life history. To know the life history of any disease requires careful clinical and pathological observation of the disease process from its earliest inception through its advanced stages. This may require years, and when dealing with intraepithelial cancer this is especially true. Carcinoma in situ of the cervix has been recognized histologically for more than forty years but its relation to invasive clinical cancer has been intensively considered only within the past decade. Even today this relationship is not fully appreciated by some pathologists or by all who are concerned with the care of patients with cervical cancer. There are still some who fail to accept the serious potentialities of this lesion. As a result of this, some physicians have recommended and carried out treatment which falls far short of our original concept of adequate therapy, namely, complete removal of the uterus. To evaluate adequately both the complete and more conservative treatment many years must pass, but we believe that sufficient time has now elapsed to produce results which can guide us in future treatment. It is the purpose of this paper to review our present information and to present additional data on the life history of carcinoma in situ of the cervix and by representative case histories illustrate how failure to apply this knowledge may lead to disastrous results.

A number of investigators have presented evidence which indicates that in some instances there seems to be a progression of changes in the cervical epithelium from normal epithelium to basal-cell hyperactivity, to intraepithelial carcinoma, and finally to invasive cancer. One of the very significant aspects of this metamorphosis is the considerable length of time which usually passes while these changes are taking place. There is doubtless considerable variation from case to case, but it seems clear from the evidence at hand that in most cases the time is measured in years for basal-cell hyperactivity finally to become clinical cancer. It must be emphasized that the view just expressed is derived largely from retrospective studies; that is to say, from studying changes in the epithelium available by chance prior to the development of invasive cancer. In those patients who have actually developed cancer,

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it can be shown that intraepithelial carcinoma pre-exists in a very high percentage of patients. Furthermore, by studying the changes prior to the development of intraepithelial carcinoma, it can be shown that basal-cell hyperactivity is present in a higher percentage of cases. It should be emphasized that this type of evidence is not helpful in determining the related question of what percentage of patients with intraepithelial cancer finally develop invasive cancer, or what percetnage of patients with basal-cell hyperactivity develop intraepithelial cancer. Therefore, the retrospective evidence about to be presented must be interpreted with these facts in mind.

Material and Methods of Study

The present paper consists of an attempt to learn more about the complete life history of cervical cancer. Three separate studies have been made:

1. A retrospective study on patients with invasive cervical cancer.
2. A retrospective study on patients with carcinoma in situ.
3. A study of the fate of a small series of women from whom a biopsy showed carcinoma in situ, but who did not receive prompt and adequate treatment for the disease.

Let us consider first 812 patients with invasive cancer of the cervix treated on our ward service in the 16 year period from 1940 to 1955. It was found that 24 of these patients had had biopsies on our service one or more years prior to the diagnosis of invasive cancer. The original biopsies when taken were not considered to be suspicious and except for local application to the cervix and an occasional cauterization no therapy was carried out. These biopsies were reviewed and in most instances additional sections were studied by recutting the original paraffin blocks. In addition, the biopsy of the final diagnosis was reviewed and the diagnosis confirmed in each case. The original biopsies were classified either as carcinoma in situ, basal-cell hyperactivity Stage I, II, or III, or no abnormality. Although the histological criteria for carcinoma in situ have been expressed many times, it is emphasized here that this diagnosis has been accepted for the purpose of this study only when the epithelial layer equals the thickness of that of the normal portio vaginalis and when the cells comprising that layer have the characteristics of malignancy with complete loss of stratification and without evidence of invasion of the underlying stroma. Basal-cell hyperactivity has been graded according to the scheme of Galvin, Jones, and Te Linde. Stage I represents only slight divergence from the normal epithelial layer, while Stage II represents the intermediate changes and Stage III closely approaches carcinoma in situ.

Part I. Epithelial Changes Preceding Invasive Cancer

Biopsy material was available in 24 cases ranging from 1 to 20 years prior to the diagnosis of invasive cancer. Of the 24 patients, 17 were thought to show the changes of carcinoma in situ. In 3 additional cases there were changes not extensive enough to be considered carcinoma in situ but sufficient to be classified by us as various stages of basal-cell hyperactivity. In only 4 cases was no abnormality noted (Table I).

Part II. Epithelial Changes Preceding Carcinoma in Situ

We have completed a parallel retrospective inquiry of those patients who have been afforded definitive therapy for carcinoma in situ in our clinic. In this study we find that during the years 1940-1955 we have treated 211 patients

for this lesion. A review of these histories shows that in 15 instances a cervical biopsy had been obtained from 1 to 10 years prior to the time of the treatment. A restudy of these 15 biopsies disclosed carcinoma in situ in 4, some degree of basal-cell hyperactivity in 10, and normal epithelium in only 1. In this latter case the initial biopsy had been obtained almost 10 years before the diagnosis of carcinoma in situ was established (Table II).

TABLE I. TIME REQUIRED FOR 24 PATIENTS TO DEVELOP INVASIVE CARCINOMA PROVED BY BIOPSY

CASE NO.	HISTORY NO.	ORIGINAL BIOPSY	INTERVAL (YEARS)	CLINICAL STAGE OF CARCINOMA
1	337893	Ca. in situ	1.0	II
2	133932	Ca. in situ	1.4	I
3	293961	B.C.H.*	1.9	I
4	437179	B.C.H.	2.5	II
5	248287	Ca. in situ	3.3	III
6	431762	Ca. in situ	3.4	I
7	203397	Ca. in situ	3.5	I
8	405452	Ca. in situ	4.5	II
9	362862	B.C.H.	4.8	I
10	132680	No abnormality	4.9	II
11	282038	Ca. in situ	5.6	II
12	117183	No abnormality	5.9	I
13	304540	Ca. in situ	6.1	II
14	299574	Ca. in situ	7.0	I
15	271214	Ca. in situ	7.7	I
16	143570	Ca. in situ	9.9	I
17	371670	Ca. in situ	11.0	I
18	277296	No abnormality	12.5	III
19	238093	Ca. in situ	13.8	II
20	147626	Ca. in situ	13.1	I
21	221077	Ca. in situ	14.8	I
22	199101	Ca. in situ	16.6	III
23	155716	No abnormality	18.0	II
24	449772	Ca. in situ	20.1	II

*B.C.H., basal-cell hyperactivity.

TABLE II. NO INVASIVE CARCINOMA SHOWN IN 15 PATIENTS IN PERIODS RANGING FROM 1.3 TO 9.3 YEARS, ALL OF WHOM EVENTUALLY HAD CARCINOMA IN SITU

CASE NO.	HISTORY NO.	ORIGINAL BIOPSY	INTERVAL (YEARS)
1	203397	Ca. in situ	2.3
2	329101	Ca. in situ	3.8
3	126609	Ca. in situ	6.6
4	520621	Ca. in situ	2.0
5	263525	B.C.H.*	1.9
6	147075	B.C.H.	2.9
7	426993	B.C.H.	3.4
8	241034	Negative	9.3
9	342958	B.C.H.	8.2
10	592301	B.C.H.	1.5
11	208325	B.C.H.	6.0
12	699487	B.C.H.	1.3
13	557069	B.C.H.	4.4
14	435613	B.C.H.	6.3
15	465191	B.C.H.	5.1

*B.C.H., basal-cell hyperactivity.

Part III. Therapy of Carcinoma in Situ

The third portion of this study was carried out in order to learn what we could of the life history of this disease from the results of therapy, complete and incomplete. During the early years of our interest in carcinoma

in situ we performed complete hysterectomy in order that the entire uterus could be studied histologically to determine the extent of the lesion. The original treatment consisted of removal of 2 cm. of parametrial tissue and about the same amount of vaginal cuff along with the entire uterus. We did not hesitate to preserve one or both ovaries in the younger patients. Since 1940 we have carried out this procedure in 211 cases. Of these patients, save for 2 who have eluded our rather meticulous follow-up system, all are living and apparently free from clinical evidence of disease.

We are acutely aware that in recent years many uteri have been sacrificed unnecessarily for supposed carcinoma in situ based upon an incorrect histological interpretation of biopsy material. Since such errors have been depicted erroneously in the literature, one cannot stress too strongly the importance of adhering to strict microscopic criteria in accepting the diagnosis of carcinoma in situ.

The question now arises whether our type of therapy is justifiable as a method of routine treatment for carcinoma in situ. Our attitude generally in gynecological surgery is conservative. We recognize the impact upon a young woman when a hysterectomy is suggested and realize that there must be sound pathological and clinical reasons when such treatment is advised. If this disease is curable by cervical cauterization, conization, or amputation in a sufficiently high percentage of cases, hysterectomy is surely out of order. Also, if because of the usually slow progress of carcinoma in situ, treatment may be withheld safely for a considerable time, prompt hysterectomy may not be indicated in all cases. There is a considerable number of cases reported in the literature in which women have remained well for many years after conization, amputation, and even cauterization. The slow course of this disease might, indeed, permit women to remain clinically well for years without any treatment. On reviewing some of the photomicrographs in certain of these cases, it is obvious that the same strict criteria for a diagnosis of carcinoma in situ have not been observed by all authors. This alone may explain the excellent results with minor therapeutic measures in many cases.

The remainder of this study concerns a series of 6 cases in which the diagnosis of carcinoma in situ was made. For various reasons, prompt treatment was not instituted, or some therapeutic measure of a lesser magnitude than total hysterectomy was carried out. The cases which are here described have come to our attention chiefly from outside sources, but one of them progressed directly under our vision. Brief summaries of these cases follow:

CASE 1.—L. M. W., No. 520621, had a dilatation and curettage for incomplete abortion at another institution in October, 1945.

The diagnosis of carcinoma in situ was made from a very small bit of tissue. The patient was referred to our clinic. She was followed from October, 1945, to October, 1951. During this time several cytological smears were made and all were found to be positive. Thirteen biopsies, two curettages, and one conization were done. We were unable to substantiate the diagnosis by biopsy until September, 1951. She was then admitted for hysterectomy. A Schiller test was done and an area found well out in the vaginal vault which did not stain. Biopsy of this area showed extension of carcinoma to the vault. This was classified by Heyman as Stage II. Irradiation therapy was given. The patient was well as of Feb. 1, 1956.

CASE 2.—R. D., No. 248287, had biopsies on March 8, April 19, and July 19, 1950, which showed carcinoma in situ. Conization was advised to obtain more tissue because there was some divergence of opinion among gynecological pathologists. This advice was not followed. She was delivered by cesarean section of a full-term pregnancy in April, 1953. Because of uncontrollable bleeding from the broad ligament, a subtotal hysterectomy was done. In July, 1953, although she was asymptomatic, another biopsy was taken. It was

positive for carcinoma in situ. A nodule was found in the left parametrium which was biopsied through the vaginal vault and found to be carcinoma, classified as cervical cancer, Stage II. Irradiation therapy was given. The patient was well as of Jan. 9, 1956.

CASE 3.—Woman's Hospital No. 48-123. On April 4 and April 8, 1950, biopsies showed carcinoma in situ at the thirty-third week of pregnancy, no visible lesion being present. Cesarean section was performed at 36 weeks. Biopsy at 4 weeks post partum from a visible lesion showed invasive cancer, Stage I. The patient was treated with irradiation followed by hysterectomy. She was well on Feb. 1, 1956.

CASE 4.—Woman's Hospital No. 59-790. On March 15, 1950, biopsy showed carcinoma in situ. The patient was also thought to have an ovarian carcinoma. Laparotomy was performed and the mass proved to be inflammatory. Because of technical difficulties, a subtotal hysterectomy was done. The patient was lost sight of and reappeared on April 6, 1952, with Stage III carcinoma of the cervix. Irradiation therapy was given. She was well as of Feb. 1, 1956.

CASE 5.—L. F., No 701491, had had a subtotal hysterectomy 20 years before. In April, 1954, a cytological smear was positive. Conization showed carcinoma in situ. The cytological smear remained positive. "Most of cervical stump" was removed. Sections showed basal-cell hyperactivity. On March 31, 1955, a cytological smear was still positive. On April 5, 1955, biopsy at The Johns Hopkins Hospital showed carcinoma in situ. A radical excision of the remainder of the cervix and the upper third of the vagina were performed. The microscopic diagnosis was cervical carcinoma with early stroma invasion. The patient is clinically well as of Dec. 1, 1956, but the cytological smear is still positive.

CASE 6.—Z. W., No. 711402, had a subtotal hysterectomy for fibroids in 1947. Biopsy on April 27, 1954, showed carcinoma in situ. Cold conization on May 3, 1954, showed carcinoma in situ with marked glandular invasion. There was questionable stromal invasion. All carcinoma was thought to have been removed. Smears were negative until January, 1955, when a positive smear was obtained. Biopsy in January, 1955, showed "squamous-cell carcinoma." X-ray therapy was given (no radium). In July, 1955, there was no clinical disease but positive smear. Multiple biopsies were negative. Two further smears were positive. Biopsy on Jan. 4, 1956, of a granular area in the vaginal vault showed invasive cancer. Radium therapy to vaginal vault was given. The patient was well as of December, 1956.

Comment

The findings of Part I of this study recorded above suggest that in the majority of cases invasive cervical cancer is preceded by carcinoma in situ or atypical changes in the cervical epithelium. The findings in Part II of this study suggest that in the majority of cases carcinoma in situ is preceded by atypical changes in the epithelium which we have chosen to designate as basal-cell hyperactivity. However, the inference must not be drawn that such atypical epithelium inevitably progresses to carcinoma in situ or that carcinoma in situ inevitably progresses to invasive cancer. It seems obvious that since these changes are usually very slow, many women will die of other causes before developing carcinoma in situ or invasive cancer. Furthermore, we believe that such progression from atypical basal-cell hyperactivity to carcinoma in situ is not the rule. We base this opinion upon an earlier study which disclosed that only 17 of 197 patients with some degree of atypicality were eventually proved to have carcinoma in situ. Our personal investigations would thus dispose us to believe that the natural history of cervical cancer encompasses a span of many years and that its development is initiated by

the appearance of atypical epithelium. However, we believe that only a small percentage of these cases progress to carcinoma in situ which *may* then advance to invasive cancer. The frequency of this latter development is still a matter of conjecture but, from the findings of Petersen and Kottmeier as well as our observations, we are inclined to believe that the percentage is appreciable if sufficient time is allowed to elapse. Petersen has recently reported 127 cases of untreated carcinoma in situ. After one year's follow-up, 4 per cent of the untreated patients had developed clinical cancer of the cervix; after 3 years, 11 per cent; after 5 years, 22 per cent and after 9 years, 33 per cent. Of the 34 women who developed invasive cancer, the lesions were microscopic in 10, Stage I in 17, Stage II in 4, Stage III in 2, and Stage IV in 1. These invasive cancers were treated, and of these 34 patients 5 were dead of cancer and one alive with recurrence at the time of this report.

Influenced by our own experience as well as that of Petersen, we have concluded that the presence of carcinoma in situ is an indication for prompt definitive therapy. Conversely, the relatively small percentage of the cases with basal-cell hyperactivity which progress to more serious lesions has led us to a very conservative attitude in dealing with these lesions clinically. In these cases biopsy and rebiopsy for as long as necessary, together with cold conization in selected cases, are greatly preferable to precipitant definitive surgery which will often prove to be unnecessary.

From the third part of this study it becomes obvious that failure of prompt treatment or failure to give adequate treatment in these cases has resulted in continued progress of the disease. In Case 1, approximately 2 years elapsed after the diagnosis of carcinoma in situ before definitive treatment was carried out and the disease progressed from Stage 0 to Stage II. In Case 2, slightly more than 3 years elapsed before the hysterectomy was done and the disease progressed to Stage II. In Case 3, no visible lesion was present at the thirty-third week of pregnancy whereas 7 weeks later a visible lesion was present and Stage I invasive cervical cancer was found. Case 4, which was lost sight of for 2 years after the diagnosis of carcinoma in situ was made, had become Stage III cervical cancer on reappearance. Case 5 progressed in slightly less than 2 years from Stage 0 to Stage I following two conizations, whereas Case 6 failed to be cured by conization and further treatment for Stage II invasive cancer was necessary 20 months after the first incomplete surgery.

Experiences like these confirm our belief that carcinoma in situ frequently develops into invasive cancer if untreated or if treated by a surgical procedure of less magnitude than a hysterectomy. It should be noted that we do not imply that this is always the case, but we believe that it does occur with sufficient frequency to indicate prompt hysterectomy. When the diagnosis is made during pregnancy, we have in all cases except one permitted the patient to complete her pregnancy. In the one exception, the lesion was so very malignant looking and it was diagnosed so early in pregnancy that we advised immediate hysterectomy. A most difficult problem arises when the diagnosis is

made in a young woman who is very desirous of a pregnancy. We are cognizant of the fact that several women have undertaken pregnancy after a diagnosis of intraepithelial cancer was made and have remained clinically well. On the other hand, in our Case 3 the lesion progressed from an invisible one, which appeared to be in situ, to a grossly visible lesion seven weeks later. We appreciate that this is most unusual and it is possible that the lesion was invasive when first judged in situ by biopsy. Our plan has been to tell these young women the facts in a completely unbiased manner. Thus far all have chosen immediate hysterectomy. If one should choose to undergo a pregnancy, it should be permitted only under the closest personal observation.

There is another experience which we have had which strengthens our belief in hysterectomy. We refer to the difficulty of evaluating the case clinically and pathologically before the entire uterus is available for study. Careful bimanual examination and conization are valuable in determining the extent of the disease but are not infallible. We have several specimens of uteri, removed because of a preoperative diagnosis of carcinoma in situ, in which there is marked glandular involvement of the cervical canal as high up as the internal os. We have 2 specimens in which the in situ lesion extends up on the surface of the endometrium to the top of the uterine cavity. In one case, myometrial invasion took place high in the uterus. It is obvious that lesions of such extent cannot be cured by cervical conization or amputation. In 2 of our cases, parametrial extension which was entirely unsuspected was found at operation.

It is the responsibility of the gynecologist to have uteri removed for carcinoma in situ thoroughly studied histologically. When fairly extensive invasion of the cervix or myometrium is found, a course of deep x-ray therapy should follow hysterectomy. When, at operation, extension beyond the confines of the uterus is encountered, the operator has the choice of changing his operative procedure to a more radical hysterectomy with complete lymphadenectomy or of closing the abdomen and treating the patient with a full course of irradiation. The decision depends upon the judgment of the surgeon after visualizing and palpating the pelvic organs from within the abdomen.

In carrying out the routine total hysterectomy for carcinoma in situ, the importance of a generous vaginal cuff should be emphasized, for even when the lesion is limited to the surface it may be quite extensive. We have had one recurrence in the vaginal vault and 3 such cases have been reported by Meigs and Graham. We now have under observation 2 postoperative cases with positive cytological smears from the vaginal vault.

Conclusion

From the evidence which has been presented, we have concluded that the unequivocal diagnosis of cervical carcinoma in situ is an indication for prompt hysterectomy with the removal of a generous vaginal cuff.

References

1. Galvin, G. A., Jones, H. W., and Te Linde, R. W.: AM. J. OBST. & GYNEC. 70: 808, 1955.
2. Kottmeier, H. L.: Carcinoma of the Female Genitalia, Baltimore, 1953, The Williams & Wilkins Company.
3. Petersen, O.: AM. J. OBST. & GYNEC. 72: 1063, 1956.
4. Graham, John B., and Meigs, Joe V.: AM. J. OBST. & GYNEC. 64: 1159, 1952.

Discussion

DR. KARL H. MARTZLOFF, Portland, Ore.—The thesis presented by the authors on therapy of cancer in situ is highly interesting. Each of the authors is so singularly well qualified to recognize the tissue changes involved in this discussion that one can immediately eliminate the necessity of raising the question of correct histologic interpretation.

Dr. Te Linde's presentation offers many interesting facets but time permits brief consideration of only three: (1) the evidence he presents to show that cancer in situ may be a preinvasive phase of cancer and, therefore, if left undisturbed may irreversibly go on to invasion; (2) the diagnostic procedures he considers essential before concluding that a given problem represents only cancer in situ uncomplicated by a coexisting unsuspected carcinoma, and (3) the thesis on which he bases his over-all recommendation of panhysterectomy —partial colpectomy when cancer in situ is diagnosed.

As Dr. Te Linde has intimated, few subjects as old as these intraepithelial carcinoid changes have remained latent so long and then have come to life so vividly now under the "nom de plume" of cancer in situ.

Since Cullen's (1900) early clear description and interpretation of this lesion which was associated with an established cancer, it has been generally accepted that these intraepithelial carcinoid changes, even when not associated with cancer, merely represent a phase in the development of cancer; therefore, cancer in its preinvasive stage. The early studies of Schauenstein (1908), Pronai (1909), Schottlaender and Kermauner (1912), and many others merely perpetuated this thought which I am sure is the point of view possessed by most of us in bygone years. While this interpretation may be correct and numerous cases have been cited which allege to prove such a sequence of events, I know of no single reported instance of where the proof submitted has appeared adequate to support such a claim.

In each of the above reported instances where cancer in situ was originally demonstrated, subsequent properly secured and adequate amounts of tissue were not promptly obtained for biopsy. Therefore, the essential ensuing histologic studies necessary to exclude with reasonable assurance the presence of a coexisting cancer were unavailable. It is my impression that the 6 cases cited briefly by Dr. Te Linde offer similar shortcomings.

Additionally, Dr. Te Linde and others state that there is a long period of latency between the development of cancer in situ and its evolution into an invasive process. To support this view two lines of argument are used. One is purely statistical, based on the difference in pages of patients with cancer in situ and those with cancer. The other is based on a series of reported cases to which allusion has just been made, where, after varying intervals, cancer followed the demonstration of cancer in situ and presumably evolved over a period of years from this intraepithelial carcinoid alteration. Dr. Te Linde's first case is used to illustrate this slow process of evolution from cancer in situ to bona fide cancer over a 6 year period. The possible presence of a coexisting but undemonstrated cancer is apparently not seriously regarded, although the biologic and clinical latency exhibited by some cancers is well known and interestingly illustrated in a case reported by Howard C. Taylor. Dr. Taylor's case was diagnosed cancer in situ on the basis of a small segment of tissue removed for biopsy. Seven years later the patient developed a full-blown cancer. Review of the original sections, however, revealed additionally an overlooked coexisting cancer.

Likewise, in our experience with 3 patients, the delay between the time a cancer was recognized, inadequately surgically treated, and its subsequent local clinical remanifestation

varied from 6½ to 10 years. Therefore, a lapse of many months or even years between the time cancer in situ is recognized and a bona fide cancer ensues does not necessarily prove that one developed from the other.

The repeated unsuccessful attempts in Dr. Te Linde's 6 cases to establish the presence or absence of cancer illustrates the general inadequacy of random punch techniques and the conventional shallow conization designed to obtain material for biopsy. The need for obtaining adequate tissue for histologic study as an immediate sequence to the diagnosis of cancer in situ is thereby emphasized. With care this can be done proficiently by conical excision of the entire cervical canal with inclusion of a liberal portion of the portio about the external os, followed by curettage of the proximal endometrial cavity. This represents generally the maximum amount of tissue obtainable for biopsy and the minimal quantity necessary for proper evaluation of the problem. Multiple longitudinal blocks and sections from the cone-shaped cervical specimen, as well as sections of the endometrial curettings, ordinarily give one sufficient tissue for adequate study. In the absence of demonstrable cancer and provided any cancer in situ that remains is well restricted to the limits of the cervical specimen, then in my experience nothing more is essential. This conclusion is based on the 15 cases of cancer in situ reported here in 1952. With one exception these patients are still well after a period of 8 to 18 years. The exception developed an adenocarcinoma of the fundus and died some years after the original diagnosis of cancer in situ. Sections of the cervix showed no neoplastic alteration. Consequently, I would hesitate to carry out Dr. Te Linde's recommendation for panhysterectomy on these or a similar group of patients.

On the other hand, when confronted by a combination of frustrating circumstances beyond one's control where, because of inadequate amounts of tissue and unsatisfactory sections, one is unable to decide histologically whether all cancer in situ has been removed or whether an area unsuitable for cytologic study may possibly represent an unrecognizable cancer, then I believe Dr. Te Linde's recommendation offers a satisfactory solution. However, in the event that the problem involves an undisclosed coexisting cancer, which probably represents the situation that occurred in Dr. Te Linde's 6 cases and possibly also in more than half of those enumerated in Table I, then the surgical procedure recommended by Dr. Te Linde seems to fall far short of an acceptable operation for cancer.

In essence, then, the problem is not just that of diagnosing cancer in situ but, of more importance, is its correct evaluation. It appears, therefore, that the crux of this discussion concerning management of cancer in situ reverts primarily to acceptably establishing the presence or absence of coexisting undisclosed cancer. Failure to observe this I believe explains most of the unsatisfactory experiences with cancer in situ.

DR. DANIEL G. MORTON, Los Angeles, Calif.—I believe that the theme which Dr. Te Linde and his associates have developed is probably correct, i.e., that full-blown invasive cancer is frequently preceded by carcinoma in situ and that the latter is frequently preceded by atypical cellular changes in the squamous lining of the cervix, but that atypical cellular changes do not invariably develop into intraepithelial cancer, nor does the latter invariably develop into full-blown cancer. There are certain considerations, however, relating to the diagnosis and treatment of so-called carcinoma in situ, which this review of experience brings to mind which have not been resolved in my opinion and these I propose to discuss briefly.

First of all, the term "carcinoma in situ" is a poor one. Its definition imposes conditions which cannot be met in a majority of instances. The definition implies that the cellular changes of the carcinoma are confined to the surface squamous lining or to the surface lining *and* the lumina of the cervical glands, without a breach of the basement membrane. Actually, it is impossible to distinguish in many instances between a mass of epidermoid cancer cells which has completely replaced the columnar cells of a gland but has not gone beyond this and a solid tongue of squamous cells which has invaded the stroma en masse. Second, the concept of a basement membrane is a very hazy one. Indeed, what is a basement membrane? Is it merely a condensation of reticulum fibers in the stroma just beneath the epithelial lining or is it something more specific, and can it be demonstrated uniformly?

It may indeed be reticulum compressed into a compact layer, but it cannot be demonstrated uniformly, even when supposedly walling off a mass of epidermoid cells in a gland lumen. In the instances in which individual cells or small clusters of cells stream off into the stroma, invasion is obvious. But in cases in which the invasion is by masses of cells, which is quite a common picture even in full-blown cancer, correct interpretation is difficult if not impossible. As a matter of fact, Dr. Te Linde was one of the first to point out that in a large proportion of cases originally diagnosed as carcinoma in situ by ordinary biopsy, more complete study of the services after hysterectomy revealed areas of minimal invasion. He makes this point again in his present paper by stating that one needs the entire cervix for completely satisfactory information.

We prefer to classify these early growths as Stage 0, which we define as that circumstance in which there is microscopic cancer only, confined to the superficial several millimeters of the cervical stroma as evidenced in a cone biopsy. We do not attempt to make a distinction based upon whether there is invasion or not, since we feel that this is often impossible and perhaps not necessary to the concept of an early confined lesion. This brings me to my second point.

It is our belief that it is not permissible to make a diagnosis of early cancer of this kind unless one has studied thoroughly all of the tissue contained in a sizable cone removed from the cervix. By "sizable" we mean a cone with a base of 2 cm. and its apex at the internal os. Such a cone cannot be obtained in the office; it requires anesthesia and usually some suturing to control bleeding. Even this amount of tissue is less than ideal but for all practical purposes, if the cancer is confined to the superficial portions of such a cone, one is justified in diagnosing it as Stage 0. According to these criteria, many cases diagnosed as carcinoma in situ in the past must remain in an uncertain classification because frankly invasive cancer was never ruled out, not enough tissue having been examined to make the exclusion.

With regard to treatment, when diagnosis has been made in the manner described, we think that it is possible to be conservative in certain instances, e.g., in young women who desire children and who are willing to be cooperative about follow-up study. Usually we employ total hysterectomy much as Dr. Te Linde has described, but practically never have we found residual tumor in the removed uterus. While this experience has been reassuring, the possibility of the development of an occasional multicentric lesion must be recognized, or of a new neighborhood lesion, so that careful follow-up for all is very important.

If my inference is correct that the diagnosis of carcinoma in situ in many of Dr. Te Linde's 211 cases was made upon the examination of far less tissue than the cone I have described, perhaps a single biopsy, four-quadrant biopsies, or perhaps even a superficial ring of tissue at the squamous-columnar junction, then I am not surprised that he found a few instances of persistent cancer. Under such circumstances I would agree that his admonition regarding the dangers of incomplete treatment are justifiable. With the larger sample of cervix, I believe conservatism in selected cases is justifiable.

DR. THOMAS C. PEIGHTAL, New York, N. Y.—The authors' studies on various degrees of anaplasia, their basal-cell hyperactivity (Stages I, II, and III) have resulted in the establishment of sound criteria for the diagnosis of carcinoma in situ. In the light of their present paper, many of us might well review again our own slides of this lesion.

One must agree that their retrospective studies have gone a long way toward demonstrating the pattern of progression from basal-cell hyperplasia to carcinoma in situ. One must agree also that from the material in this paper they are fully justified in the conclusion that "the unequivocal diagnosis of cervical carcinoma in situ is an indication for prompt hysterectomy with the removal of a generous vaginal cuff."

In addition the authors are to be complimented upon the favorable outcome to date of the 6 cases reported in detail as evidencing the problems which may arise when, for one reason or another, hysterectomy has not been done.

The degree to which we find ourselves in any disagreement with the essayists is small but, at the same time, significant. We prefer to use the cytologic smear to indicate the need for biopsy study. Also we feel we secure more detailed information from an extensive cone biopsy or partial amputation with multiple section study of the specimen. Early stromal invasion is better detected thereby and treatment can be planned to suit the lesion. We note that in their later cases the authors used the cold conization biopsy too.

In our clinic, for the most part, carcinoma in situ cases diagnosed by this method have been treated by hysterectomy. If, however, as rarely happens, any patient should not come to hysterectomy, she is followed closely by cytologic smears and re-evaluated for surgery if they become positive.

In 1954, we reported upon 15 patients with carcinoma in situ who had nothing more than extensive cone or amputation of the cervix. To within the past few months 9 have been just over 3 years, 2 have been 4 years, and 4 have been 5 years since the cone or amputation procedure. Two, aged 25 and 28 years at the time of treatment, have had one child each.

We present these examples of conservative treatment as a matter of observation and in no sense meaning to take issue with the present essayists and their conclusions. We still believe the treatment of carcinoma in situ is hysterectomy but we also feel that on rare occasions certain circumstances do arise when one may be justified in doing cervical amputation with closely guarded follow-up by cytologic smear. This is a calculated risk which some young patients will wish to take and which the gynecologist should be prepared to manage with confidence.

DR. ROGER B. SCOTT, Cleveland, Ohio.—I wish to add one thing and possibly reinterpret something that was said and has gone down in the literature on which Dr. Te Linde has changed his mind. Many years ago he was of the opinion after studying these lesions very carefully that a large percentage of them showed invasion. At that time he used the term "invasion" for glandular involvement. He has changed his mind about that and feels that this is a glandular involvement and not true stromal invasion. It is unfortunate that his first opinion is still being quoted. I hear it repeatedly and I hope he will not take offense at this statement, quoting from Robert Meyer: "A man is never old as long as he can change his mind and change his pants while standing up." And Dr. Te Linde did change his mind.

When there is a lesion high in the cervical canal, a punch biopsy is not adequate to determine what is going on. We must have a more extensive sample. Even when we have a full sample, such as a sharp cone, we still are not always certain as to invasion. Unfortunately, there is no such thing as a basement membrane; it has never been stained or demonstrated; it does not exist as such. We feel that when there is involvement more than 3 mm. below the endocervical surface, then there probably is true invasion. At any point not beyond 3 mm., opinions may differ. I agree very strongly with the advice that a full, wide hysterectomy be done for carcinoma in situ, including a wide vaginal cuff. There is also a conservative approach in certain instances. With a wide hysterectomy and adequate vaginal cuff we are not in the position of having done inadequate surgery for a lesion which may eventually prove to be invasive. Lymph nodectomy or x-irradiation can be performed subsequently.

DR. RONALD R. GREENE, Chicago, Ill.—I do not think that anyone would disagree that the ideal therapy, when one gets a moderately atypical or suspicious or positive smear, is to hospitalize the patient and do a cone—if the patient can afford it. But I object to the idea on a semantic basis, if you will. We are endeavoring to train our medical students to biopsy the cervix at the drop of a hat. It is a very simple office procedure. Four-quadrant biopsies give a good idea of the extent or presence of a lesion—and please note that in a properly done biopsy at least half of the tissue is ectocervix and the other half endocervix. Recently we have not used the Schiller test, but we should. I am sure that in many

of these cases of moderately atypical tissue we probably would not do anything except follow up with smears and repeat biopsies because the patient cannot afford hospitalization and the surgical procedures necessary for a cervical cone.

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pa.—I wish to support those who are thinking in terms of the safety of their patients. I do not speak for those who merely sample a cervix from which has emanated a positive carcinoma cell as discovered in the smear. This, however, is not my main reason for being here. I want to point out that I cannot do a "little bit more hysterectomy" and get the 2 cm. of parametrium to which Dr. Te Linde referred without lifting the ureters from their tunnels. I cannot get the 2 cm. of parametrium nor more than 1 cm. of vaginal cuff without so lifting the ureters. I should like to ask the distance in Baltimore between the side wall of the cervix and the ureter?

DR. NORMAN F. MILLER, Ann Arbor, Mich.—I am amazed to hear the diversity of opinion and also to discover how people can reconcile in their own minds a conservative treatment on the one hand and radical treatment on the other, all by the same individual with a single philosophy regarding the lesion. I am certain that this discussion has not extended too long but I am equally certain that it should be continued at another time.

DR. TE LINDE (Closing).—Dr. Martzloff will be surprised when I agree with him. I do not think any clinical evidence is ever 100 per cent conclusive. I simply presented our clinical experience. I think it is enough to make us think that this is a serious lesion.

Dr. Morton stressed the difficulty of determining whether invasion is present and we have thought about that a great deal. I have not changed my mind; I have only changed my terminology. In our first paper when we spoke of glandular invasion we meant the same thing as we do now when we speak of glandular involvement. We mean the growth of this abnormal tissue into the gland. It is difficult to get any two pathologists to agree as to just where extensive glandular involvement ends and true invasion begins.

I like Dr. Morton's Stage 0 and we use that term clinically to indicate cases of in situ carcinoma or very early microscopic invasion. Carcinoma in situ is a histologic term and it applies only to the bit of tissue under the microscope in that particular field. It can be adjacent to an invasive cancer or it can be all that is present.

I remember that Dr. Peightal showed us some of his sections in New York. I saw them only as lantern slides but many that he treated with less than hysterectomy would not meet our criteria of carcinoma in situ. That is why I think there is so much difference of opinion about treatment—because there are different criteria for diagnosis. Most of the cases he treated with conization we would say represented only basal-cell hyperactivity and we would get more information before treatment.

In regard to hysterectomy, this is what we do with young people. Take a girl of 26, for instance, in whom we have made the diagnosis. I would be perfectly willing under the closest observation to follow her and let her have her pregnancies, but I would want to be sure of the cooperation of the patient. We put the facts up to the patient and so far they have all decided to have hysterectomy and adopt their babies. At Duke University many of these young women have chosen to have babies.

Dr. Kimbrough wants to know how to do this "little more hysterectomy" and I would be very glad to show him if he would come down to Baltimore. The ureters are catheterized preoperatively, which is a great help. Dr. Kimbrough also asked me the distance between the side wall of the cervix and the uterus, and that is like asking me the capacity of a balloon. You can move a ureter laterally to some degree without dissecting it from its tunnel or disturbing its blood supply.

FOLLOW-UP ON CERVICAL EPITHELIAL ABNORMALITIES*†

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THE concept of preinvasive squamous-cell carcinoma of the cervix has become firmly established in recent years though the criteria for the diagnosis of this lesion vary somewhat from person to person and place to place. The widespread interest in this lesion plus the increased use of vaginal and cervical smears as a screening procedure have made it evident that there is a whole spectrum of lesser abnormalities which lie in the continuum between normal epithelium and preinvasive carcinoma. It has been suggested that these changes may represent steps in a progression from the normal to preinvasive carcinoma. These lesions have been variously designated as anaplasia, atypical hyperplasia of the stratified squamous epithelium, basal-cell hyperplasia, and by many other terms. We have used two terms to describe these abnormalities: atypical basal-cell hyperplasia and equivocal lesion. The latter term is used by us when abnormalities extend throughout the full thickness of the epithelium but are inadequate to justify the diagnosis of preinvasive carcinoma. The former is reserved for instances where such abnormalities are restricted to the lower one half to two thirds of the epithelium, the superficial layers remaining normal.

In an attempt to assess the significance of such lesions we have reviewed all such specimens from the Departmental Laboratory at Northwestern University Medical School. Nine hundred ninety-two specimens from 489 patients were considered to fulfill the criteria for one or the other of these diagnoses. The patients came from a variety of sources (Table I) and, in general, were rather highly selected on the basis of abnormal cervical smears. The private patients, for the most part, were seen by members of the Department of Obstetrics and Gynecology at Northwestern University Medical School and included, therefore, both obstetrical and gynecological patients. Those from the Northwestern Medical School Clinics were likewise mixed, while those from the Chicago Maternity Center and Cook County Hospital were preponderantly obstetrical.

The great majority of the specimens were biopsies of the four-quadrant type made with either a Gaylor or Schubert instrument. A lesser number were cold-knife cone amputation or hysterectomy specimens which precluded further follow-up (Table I).

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TABLE I. MATERIAL

SOURCE	NO. CASES	FIRST TISSUE HYSTEREC-TOMY OR CONE	WITHOUT FOLLOW-UP BIOPSIES	WITH FOLLOW-UP BIOPSIES	PER CENT WITH FOLLOW-UP*
Private	192	26	102	64	38.6
Northwestern	84	2	29	53	64.6
Chicago Maternity Center	134	0	35	99	73.9
Cook County Hospital	79	0	53	26	32.9
Total	489	28	219	242	52.5

*Exclusive of Column 2.

*Age Distribution.**—The age distribution of these patients at the time of first tissue examination is shown in Fig. 1. Over half (256) were between the ages of 20 and 35 years. The unusually large number of young patients in this group is easily explained by the fact that 43.6 per cent of the total group came from predominantly maternity clinics where the majority of patients were Negro. The age distribution of this patient population is that of pregnant patients in the low-income group (Fig. 2). This weighting by pregnant patients also occurs in the private group but is less pronounced. Estimates of age distribution of *all* patients seen in the various clinics (Fig. 2) show that the age distribution of the 489 patients with lesions merely reflects that of the patient population from which they were selected. However, these data do emphasize the fact that such lesions will be found in young women if they are screened by smear and/or biopsy.

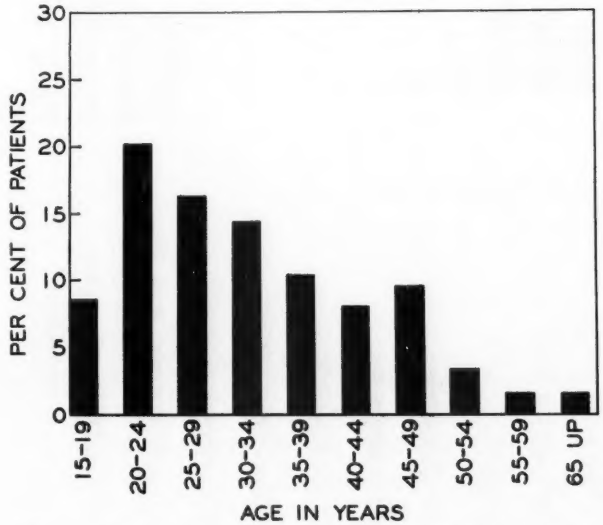


Fig. 1.—Age distribution of 489 patients with lesions.

Follow-Up.—Two hundred forty-two patients had more than one tissue examination and of these 125 were subjected to biopsy three or more times, 63 four or more times, and 29 six or more times. One cooperative soul has been

*The estimate of the age distribution of private patients is based on random selection of 500 patients from the cervical smear records in the departmental laboratory for private patients. As practically all private patients seen by members of the department are subjected to routine cervical smears, this should give a relatively accurate estimate. The age distribution of patients attending the Northwestern Clinics was roughly estimated on the basis of 250 consecutive admissions. An estimate of the age distribution of patients attending the Chicago Maternity Center was obtained by determining the ages of the first 10 patients who were delivered each month in the years 1952 through 1954, inclusive. The ages of the patients in the Cook County Hospital group were obtained as part of a study designed to determine prevalence of cervical abnormalities in pregnant patients. The ages of 503 randomly selected patients were available and formed the basis of this estimate.

subjected to biopsy 13 separate times in a space of eight years! One hundred and two of these 242 patients were followed for 12 months or more, 48 for 24 months or more, and 24 from 36 to 97 months (Table II).

TABLE II. LENGTH OF FOLLOW-UP, 242 PATIENTS

Under 12 months	140
12 months and over	102
24 months and over	48
36 months and over	24
48 months and over	11

One hundred thirty-three of these patients had an original diagnosis of atypical basal-cell hyperplasia and 109, a diagnosis of equivocal lesion. The results of follow-up are presented in Table III. As might be expected, the number of cases which reverted to negative or normal is highest in the atypical basal-cell hyperplasia group and the number which progressed to preinvasive carcinoma is greatest in the equivocal group. If only regression and progression from the original lesion are considered, the percentages are about the same

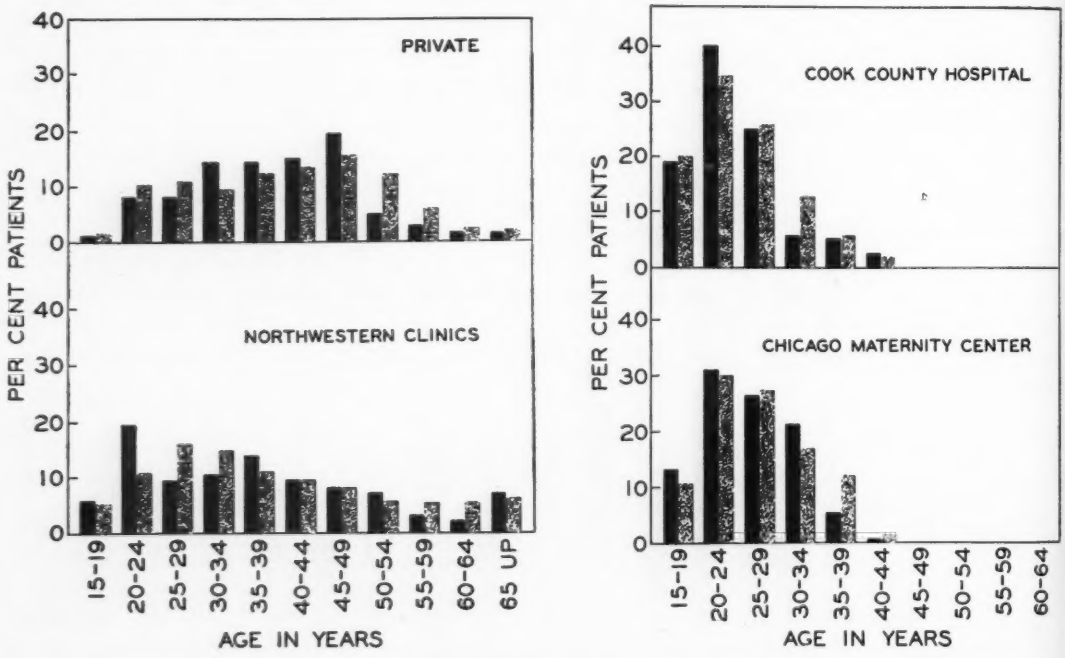


Fig. 2.—Comparison of age distribution of patients with lesions and estimated age distribution of all patients seen for each patient source. The solid columns represent the patients with lesions in each instance.

for the two groups (49.6 compared to 54.2 per cent and 15 to 16.5 per cent, respectively). When these 242 cases were considered as one group and the result of the final tissue examination was viewed as either negative, abnormal, preinvasive, or invasive carcinoma (Table IV), 40.5 per cent were negative, 48.8 per cent abnormal, 10.3 per cent preinvasive carcinomas, and 0.4 per cent (one) invasive carcinoma.

Seventeen, or 65 per cent, of the 26 which "progressed" to preinvasive or invasive carcinoma were found after less than one year of follow-up. It

seems likely that most, if not all, of these were co-existing lesions actually present at the time of the original biopsy. The details of follow-up on the 9 patients in whom carcinoma was found and who were followed for one year or more are diagrammed in Table V. Six of the 9 were followed 15 months to 56 months before a biopsy showing preinvasive (invasive in one) carcinoma was obtained. It is interesting that 5 of the 9 had negative four-quadrant biopsies prior to and, in one instance, after the finding of preinvasive carcinoma, indicating that a negative biopsy should not terminate follow-up. Three of these 9 patients were treated by hysterectomy and one by radiation. The remaining 5 were untreated at the time of tabulation.

TABLE III. RESULT OF FOLLOW-UP ACCORDING TO ORIGINAL BIOPSY DIAGNOSIS

DIAGNOSIS	ATYPICAL BASAL-CELL HYPERPLASIA		EQUIVOCAL LESION	
	NO.	%	NO.	%
Number of patients	133		109	
Negative	66	49.6	32	29.4
Regression to atypical basal-cell hyperplasia	–		27	24.8
No change	47	35.4	32	29.4
Progression to equivocal lesion	12	9.0	–	
Preinvasive carcinoma	8	6.0	18*	16.5

*One invasive carcinoma included.

TABLE IV. RESULT OF FOLLOW-UP, ENTIRE GROUP

FINAL TISSUE DIAGNOSIS	LENGTH OF FOLLOW-UP					
	UNDER 12 MONTHS		12 MONTHS AND OVER		ALL PATIENTS	
	NO.	%	NO.	%	NO.	%
Negative	44	31.4	54	53.0	98	40.5
Abnormal	79	56.5	39	38.2	118	48.8
Preinvasive Ca	17	12.1	9*	8.8	26*	10.7
Total	140	100.0	102	100.0	242	100.0

*One invasive carcinoma included.

The ninth patient in this group (H. E.) is of interest as the final biopsy showed invasive carcinoma (Stage I). When first seen in 1949 the patient was pregnant. Because of an irregular eroded cervix, biopsy was made and an equivocal lesion (Fig. 3) noted. The patient did not return and could not be located until 1953. Again she was pregnant. Smear and biopsy were positive for carcinoma (Fig. 4, *A* and *B*). Grossly there was no obviously malignant lesion but the embolus in the lymph gland seems to leave little doubt as to the invasive nature of the tumor. The patient was treated by deep x-ray therapy and radium insertion after interruption of the pregnancy (in the sixth month) and is apparently well at present.

In an additional 12 (7 with equivocal lesions and 5 with atypical basal-cell hyperplasia) of the 242 patients the diagnosis of preinvasive carcinoma was made in a follow-up biopsy but not confirmed in subsequent tissues. Five of these patients were treated by hysterectomy or cone, serial blocks of the cervix being made. Equivocal lesions were found in 4 and atypical basal-cell hyperplasia in the fifth. In another the hysterectomy specimen was not available to us. In the remainder the last biopsies were negative in 2, atypical basal-cell hyperplasia in one, and equivocal in 3. One of these latter is still being followed after 13 biopsies during an 8 year span (A. G., No. 3 of our previous

report[5]). After the diagnosis of preinvasive carcinoma was made at 43 months, two negative biopsies were obtained at 59 and 79 months, with an equivocal lesion at 97 months.

TABLE V. DETAILS CONCERNING 9 PATIENTS WITH FINAL DIAGNOSIS OF PREINVASIVE OR INVASIVE CARCINOMA FOLLOWED FOR 12 MONTHS OR MORE

CASE NO.	PATIENT	BIOPSY NO. 1	2	3	4	5	6	7	8
1	R. J.	Equiv.	Ca. 12						
2	H.	BCH	Equiv. 7	Ca. 12					
3	E. J.	BCH	Neg. 3	BCH 10	Ca. 16	Ca. Hyst. 20			
4	C. P.	Equiv.	Equiv. 5	Ca. 7	Neg. 8	Equiv. 17	Ca. 23		
5	A. B.	BCH P	Ca. 25						
6	G. D.	Equiv.	Neg. 3	Neg. 9	BCH 21	Equiv. 21	Ca. 27	Ca. Hyst. 32	
7	L. R.*	BCH	BCH 1	Equiv. 6	Neg. 13	Ca. 15	Ca. 27	Ca. Hyst. 32	
8	S. C.*	Equiv. P	Equiv. 1	Neg. 8	Equiv. 14	Neg. 23	Equiv. 28	Neg. 38	Ca. 51
9	H. E.	Equiv. P	Invasive Ca. 56	Invasive Ca. 57					

Equiv. = equivocal lesion.
Ca. = preinvasive carcinoma.
BCH = atypical basal-cell hyperplasia.
Hyst. = hysterectomy.
P = pregnant at first biopsy.
The number beneath the result of biopsy refers to the number of months after the first biopsy.
*Patient S. C. is No. 14 and Patient L. R. is No. 20 of a previous report.[5]

TABLE VI. RESULT OF FOLLOW-UP ON PATIENTS PREGNANT AND NONPREGNANT AT TIME OF ORIGINAL DIAGNOSIS

FINAL TISSUE DIAGNOSIS	PREGNANT* NO.	%	NONPREGNANT* NO.	%
Negative	24	34.8	74	42.8
Abnormal	37	53.6	81	46.8
Preinvasive carcinoma	8†	11.6	18	10.4
Total	69	100.0	173	100.0

*Differences between pregnant and nonpregnant groups are not statistically significant.[2]
†One invasive carcinoma included.

Pregnancy.—Sixty-nine of the 242 patients with follow-up were pregnant at the time of the original diagnosis and 173 were not pregnant. The over-all disappearance rate of the abnormal epithelium was 34.8 per cent in the pregnant patients and 42.8 per cent in the nonpregnant (Table VI). The persistence rate was 53.6 per cent in the pregnant and 46.8 per cent in the nonpregnant. Carcinoma was ultimately found in 11.6 per cent of the pregnant group

and 10.4 per cent of the nonpregnant group. These differences between the pregnant and nonpregnant groups were not significant.* Further division of these groups (Table VII) does not disclose statistically significant differences though the groups are somewhat small for trustworthy analysis.

TABLE VII. RESULT OF FOLLOW-UP ON PATIENTS PREGNANT AND NONPREGNANT AT TIME OF ORIGINAL DIAGNOSIS ACCORDING TO LENGTH OF FOLLOW-UP

FINAL TISSUE DIAGNOSIS	UNDER 12 MONTHS				12 MONTHS AND OVER			
	PREGNANT*		NONPREGNANT*		PREGNANT*		NONPREGNANT*	
	NO.	%	NO.	%	NO.	%	NO.	%
Negative	5	13.5	39	37.8	19	59.4	35	50.0
Abnormal	27	73.0	52	50.5	10	31.2	29	41.5
Preinvasive carcinoma	5	13.5	12	11.7	3†	9.4	6	8.5
Total	37	100.0	103	100.0	32	100.0	70	100.0

*Differences between pregnant and nonpregnant are not significant by chi square analysis with Yates correction for continuity.[2] The small numbers in the pregnant group make analysis of questionable value.

†One invasive carcinoma included.

These data suggest that these abnormalities, whether discovered during pregnancy or in the nonpregnant patient, behave in a similar manner in regard to their subsequent course. For this reason it seems likely that they are not evanescent "pregnancy changes."

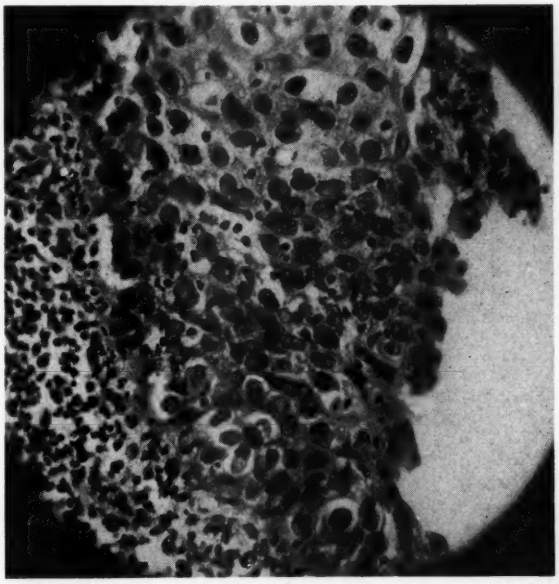


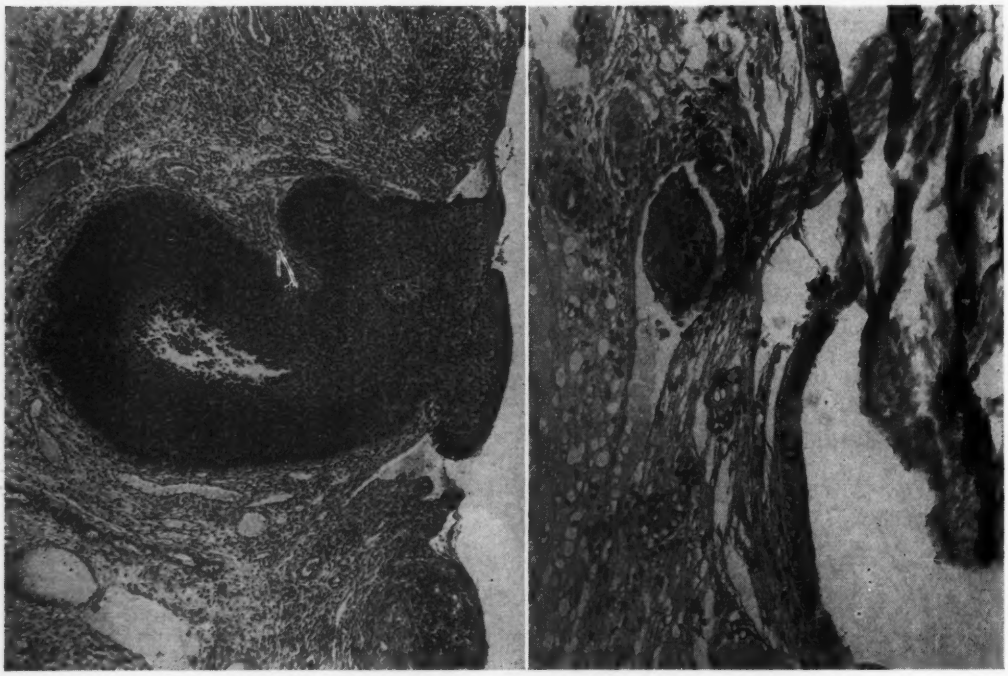
Fig. 3.—NU No. 10992. Patient H. E. Equivocal lesion discovered during pregnancy in 1949.

Comment

This study has all the deficiencies of such biopsy investigations so clearly set forth by Galvin, Jones, and Te Linde.[1] The microscopic interpretations are subjective and will vary to some degree from observer to observer. The area sampled is small; coexisting lesions may be missed and small lesions may be completely destroyed. Reagan and associates[7] and others[8] are using cytology

*Probability > 0.70, chi square analysis.[2]

studies in an attempt to obviate these latter difficulties. Reagan states that correlated cellular and tissue studies give reason to believe that the cytology method, used alone, is acceptable as a follow-up procedure for such lesions. Our experience has not paralleled theirs. In the 76 instances where smear and biopsy were done at the same time during follow-up on the 109 equivocal lesions in this study exclusive of the original examination, there was agreement in only 47, or 61.9 per cent. In 13 instances (17.1 per cent) the biopsy was negative and the smear was abnormal, indicating the presence of an abnormality. However, in 16 (21.0 per cent) the smear was negative but the biopsy



A. *B.*

Fig. 4.—*A*, NU No. 19536. Patient H. E. Cervical biopsy showing squamous-cell carcinoma in an endocervical gland 56 months later, the patient again being 6 months pregnant. *B*, NU No. 19536. Patient H. E. Adjacent area from biopsy in *A*, showing invasion of lymph gland.

revealed an abnormality (9 atypical basal-cell hyperplasia and 6 equivocal lesions). In one instance in this small group the smear was negative in the presence of preinvasive carcinoma. These data suggest to us that a single negative smear does not exclude the possibility of the presence of such a lesion and should not be interpreted as incontrovertible evidence of regression. It is also true that the four-quadrant biopsy method can and does occasionally miss small lesions. This probably explains some of our apparently inconsistent findings with repeated biopsies on the same patient.

Comparison of the results of follow-up in studies of this type is difficult because of differences in the method of collection of data, selection of patients, and of presentation. With these limitations in mind we have recomputed the

data concerning the 65 patients of Reagan and co-workers, the 191 patients reported by Galvin and associates, and our 242 patients. If the 35 patients in Galvin's Stage III category are excluded, the results are strikingly similar (Table VIII). The combined data show regression in 51.4 per cent, no change in 31.8 per cent, and progression in 16.8 per cent. If the 35 patients in Galvin's Stage III group are included, the percentages for their data alone become 44, 28.2, and 27.8, because of the fact that 23, or 67 per cent, of this group progressed to preinvasive carcinoma. It is possible that the criteria of Galvin and co-workers for preinvasive carcinoma are more strict than ours (see Galvin's Figs. 3 and 4) and that some of their lesions classed as Stage III would have been considered preinvasive carcinoma by us.

TABLE VIII. COMPARISON OF RESULTS OF FOLLOW-UP

	STAGES I AND II* GALVIN ET AL.	REAGAN ET AL.[6]	OUR DATA†	COMBINED DATA
No. of patients	156	65	242	463
Regression	50.0%	53.8%	51.7%	51.4%
No change	30.8%	30.8%	32.6%	31.8%
Progression	19.2%	15.4%	15.7%	16.8%

*Computed from data in Table II, Galvin and associates.[1]
†Computed from data in Table III.

Nesbitt's[4] findings in a group of 255 patients with basal-cell hyperactivity found during pregnancy or immediately post partum cannot be directly compared with our data because of differences in tabulation. However, our results do not support the conclusion that 94.1 per cent of cases of basal-cell hyperactivity discovered during pregnancy revert to normal by the sixth month post partum. Our findings are similar to those of Rawson and Knoblich[6] in that the incidence of abnormalities eventually associated with preinvasive carcinoma, or with regression to normal, was the same whether the patient was or was not pregnant at the time of the original biopsy.

Summary and Conclusions

Of 489 patients found to have epithelial abnormalities insufficient for the diagnosis of preinvasive carcinoma, 242 had one to 13 follow-up biopsies, for the most part of the four-quadrant type. A small number had hysterectomy or cone amputation of the cervix. Of these, 133 were given an initial diagnosis of atypical basal-cell hyperplasia and 109 were considered to have equivocal lesions. In 40.5 per cent of these patients the lesion could not be found at the last tissue examination. In 48.8 per cent abnormalities persisted and in 10.7 per cent preinvasive carcinoma (there was one invasive carcinoma) was ultimately found. Twelve, or 5.0 per cent, at some time during follow-up had a tissue diagnosis of preinvasive carcinoma that was not found on subsequent tissue examination.

Sixty-nine of these patients were pregnant at the time of the original diagnosis and 173 were not pregnant. The disappearance rate was 34.8 per cent in the pregnant and 42.8 per cent in the nonpregnant. The persistence rate

was 53.6 per cent in the pregnant and 46.8 per cent in the nonpregnant. Carcinoma was present in the last biopsy in 11.6 per cent of the pregnant group and 10.4 per cent of the nonpregnant group. These differences are not statistically significant.

These data are compared with similar data from the literature, and with necessary reservations the differences are discussed.

Our patients have not been followed for sufficient time to permit conclusions as to the eventual outcome of such lesions. Our data do indicate, however, that these lesions occur in young women and that there is no significant difference demonstrable in the behavior of these lesions whether found in the pregnant or nonpregnant patient.

References

1. Galvin, G. A., Jones, H. W., and Te Linde, R. W.: Am. J. Obst. & Gynec. **70**: 808, 1955.
2. Guilford, J. P.: Fundamental Statistics in Psychology and Education, ed. 2, New York, 1950, McGraw-Hill Book Company.
3. Jordan, M. J., Bader, G. M., and Day, E.: Am. J. Obst. & Gynec. **72**: 725, 1956.
4. Nesbitt, R. E. L., Jr.: Obst. & Gynec. **6**: 239, 1955.
5. Peckham, B., Greene, R. R., Chung, J. T., Bayly, M. A., and Benaron, H. B. W.: Surg., Gynec. & Obst. **99**: 401, 1954.
6. Rawson, A. J., and Knoblich, R.: Am. J. Obst. & Gynec. **73**: 120, 1956.
7. Reagan, J. W., Hicks, D. J., and Scott, R. B.: Cancer **8**: 42, 1955.

Discussion

DR. LOUIS M. HELLMAN, Brooklyn, N. Y.—It is now generally accepted that a variety of progressive and regressive changes occur in the cervical epithelium in response to a host of stimuli. These vary from simple hyperplasia of the basal layer through all stages of abnormal cellular response, even to invasive carcinoma. The natural history of these changes is of great current interest and fundamental to further understanding of the genesis of cervical malignancy.

Dr. Peckham has attempted to supply information concerning two very important aspects of this subject, namely, the degree of regression of these lesions and the influence of pregnancy upon the frequency of this regression. Certainly, from the standpoint of the patient's well-being, no more important questions could be asked.

The life history of basal-cell hyperactivity and equivocal lesions in the stratified squamous epithelium have been studied. While this classification into two categories is broad, the description and fine photomicrographs make clear the specific pathologic changes under discussion. Within the limits of the sample, the author has shown that not only do regression and progression occur, but the frequency of regression is correlated with the severity of the initial lesion. Furthermore, his data make quite clear that in this specific sample there is no difference in the frequency of regression in the pregnant and nonpregnant patient. This latter observation is in contrast with that of Nesbitt, who showed a significantly higher incidence (94 per cent) of regression after pregnancy. Pathologic knowledge has reached a level where there can be little argument concerning the validity of such findings by competent investigators. The discrepancies, therefore, must stem either from the sample studied or the location of the lesion.

Dr. Peckham's sample consists of a group of women subjeced to biopsy on the basis of abnormal cervical smears. The study is in reality a retrospective one, for it is based on the material on hand and not pre-selected according to a particular plan. That there happened to be a certain number of pregnant patients in the sample was almost fortuitous. From the standpoint of a study of these changes in pregnancy, particularly with the view to comparison with those in nonpregnant individuals, such selection is susceptible to marked bias. It is quite probable that the pregnant patients were screened early in gestation and, therefore, might have

had pre-existing epithelial lesions on an entirely different basis which might well indefinitely outlast the pregnancy. It might well be that this is the reason for the large discrepancy in the frequency of the regression to normal between this study and that of Nesbitt. In the latter, because the research was prospective, with a view to studying epithelial changes as related to pregnancy, biopsies were taken throughout the course of gestation. This planning increased the size of the sample and by so doing, if pregnancy had anything to do with the change, increased the frequency of regression. The difference in results between the two studies might prove rather than disprove the point.

Trauma, infection, and hormones, particularly estrogen, activate the cervical epithelium by stimulating the growth of the basal cells. The epithelium of the endocervical canal is far more responsive to hormone stimulation than that of the ectocervix. In the latter, while smears show typical hormonal changes, it is difficult to correlate these with biopsy material and changes in the basal cell are equivocal. The situation is quite different in the canal, for the basal cell here is much more primitive, more responsive to hormones, and multipotential. Response to hormone stimulation is marked, especially if the stimulus is applied when cyclic ovarian activity is in abeyance, as in pregnancy or after the menopause. These changes in the canal can be classified in much the same manner as those in the ectocervix, namely, typical and equivocal, but because they are hormonally instigated they are much more likely to be evanescent. Dr. Peckham's studies are concerned with the stratified squamous epithelium of the ectocervix, thus minimizing those specifically related to pregnancy.

These statements are not in criticism of the present study for it seems to me that Dr. Peckham has, within the limits imposed by his material, answered the question of regression and progression. If, however, we are to advance our knowledge from this point, future studies must be prospective and pointed particularly at the effect of specific stimuli at specific locations.

DR. ARTHUR B. HUNT, Rochester, Minn.—During a 5 year period ending Jan. 1, 1957, there were 137 patients with basal-cell hyperactivity, and during this time about 60,000 separate patients had cytologic smears which gives an incidence of basal-cell hyperactivity of about 0.25 per cent. In this same period there were about 10,000 cervical biopsies, which gives us an incidence of about 1.4 per cent incidence of basal-cell hyperactivity but many of these biopsies are repeat biopsies. The incidence frequently quoted of basal-cell hyperactivity is from 1.8 to 3.1 per cent for nonpregnant individuals.

Ten of the 137 patients had carcinoma in situ. Five of these 10 were found by further investigation at the time of first admission, and 5 from 3 to 36 months later. There were 2 instances of invasive carcinoma, both found by further investigation at the time of the first admission. This gives an incidence of 8.8 per cent as compared to the authors' quite similar incidence of 10.7 per cent.

Sixty of our cases were followed throughly by smear and biopsy or had definitive therapy, such as hysterectomy for carcinoma in the 12 cases or hysterectomy for other gynecologic disease. In the remainder a thorough conization or cauterization was performed, or definite arrangements were made for follow-up through referring physicians in all save 14 cases. Leukoplakia appeared along with basal-cell hyperactivity in 12 patients, and 3 of these had carcinoma in situ. Seven, or 5 per cent of the entire group, had basal-cell hyperactivity in cervical stumps, and one of the 2 invasive carcinomas occurred in a stump. The regression rate as well as the incidence of carcinoma was very similar to that reported by Drs. Peckham and Greene and others.

The authors have shown in this presentation and in formers ones that, with critical examination, pregnancy does not materially change the situation as far as regression to a normal cervix and progression to carcinoma in situ is concerned in spite of a few opinions to the contrary.

These patients with basal-cell hyperactivity deserve meticulous follow-up, and those that neither progress nor regress may need this observation for a *long* period of time to do them

justice. The American population is more nomadic than in most countries and when we add those *young* women who are being allowed to have at least a curtailed reproductive career with preinvasive carcinoma, the follow-up responsibility in the future may be a real burden.

Our records in the 5 years referred to also show reports of 4 cases wherein the report of basal-cell hyperactivity appeared in the follow-up of patients treated conservatively for carcinoma in situ by thorough cautery or conization. Three of these 4 were so treated to allow pregnancies, and these 3 patients have had five children and one is currently pregnant, all with negative cervices on both biopsy and smear at the last several examinations. The fourth patient had an extreme fixation of the uterus following operation for carcinoma of the colon and likewise has a negative cervix postcautery with a 2 year follow-up.

Drs. Peckham and Greene have follow-up information on 242 cases, or slightly less than half of their total group of 489 patients. I would covet for the other half as good a follow-up, since 10 per cent developed preinvasive or invasive carcinoma and I think, as nearly as possible, our follow-ups should be universal until it seems evident that the cervix will remain negative on biopsy or at least consistently negative on smear. I say this in spite of the fact that at least 10 per cent of our series was not accorded a proper follow-up.

It is disturbing and pertinent to note that, in 5 of Dr. Peckham's 8 patients who developed preinvasive carcinoma, there were negative biopsies interspersed throughout the follow-up so that one negative biopsy or even two in sequence do not guarantee freedom from development of carcinoma in situ in the future. This was not true in our experience as all 12 patients maintained abormal cytologic smears and/or biopsies prior to the diagnosis of preinvasive or invasive carcinomas.

DR. CARL T. JAVERT, New York. N. Y.—I have two questions to ask and they are in reference to the 242 patients who were followed.

First, how many were ultimately treated by total hysterectomy, and, second, how often was the cytologic smear used in the follow-up of these patients? There is a limit to the number of biopsies one can take from a cervix in the course of an extensive follow-up. It has been my privilege to be associated with two institutions in New York where cytology had its origin—the Women's Hospital and the New York Hospital. I think, as a result of Papanicolaou's work, most of us last night and today have been thrown into a dilemma by an increasing number of atypical lesions of the cervix. We are hard put as to their proper treatment. There seem to be two schools of thought: one likes to follow these patients and the other is inclined to be more radical. At the New York Hospital, where for 10 years I have had the opportunity to correlate the histologic material with the Papanicolaou smear, I have seen negative biopsies and positive smears, and on Dr. Papanicolaou's insistence we have done hysterectomy and have found carcinoma either in the endocervix high in the canal or in the endometrium or even the Fallopian tubes. During that period of time I have seen perhaps 50 hysterectomies done because of a suspicious biopsy or smear, or a positive biopsy and suspicious smear, or a positive smear and negative biopsy. During the same time interval some 2,500 hysterectomies have been done for benign disease. So I feel pretty certain that if we are confronted with this problem we should do a total hysterectomy and that is why I asked the question relative to the number performed by Dr. Peckham.

Finally, I would like to mention a patient, aged 42, operated upon in 1947 for early carcinoma in situ. Dr. Marchetti read the sections and made the original diagnosis. This was confirmed by the pathologists at the Memorial Hospital. She was then treated by cervical amputation. The surgeon subsequently died and her follow-up was cluttered. Two years later she had some more bleeding and went to Dr. Brunschwig who completed her hysterectomy, did a lymph node dissection as well, and found one positive node. She is alive ten years later. In gratitude she gave Memorial Hospital a laboratory costing $750,000. But she did not give anything to the New York Hospital where the initial diagnosis was made by Dr. Marchetti.

If I may be permitted a witticism this morning I would say: "When in doubt, take it out."

DR. PECKHAM (Closing).—Really this was not entirely a retrospective study as we had originally planned to follow as many of these patients as possible, although we did assemble these patients from the departmental files in a retrospective manner years later. The patients who were pregnant were in all stages of pregnancy and no attempt was made to divide them into trimesters of pregnancy to see if such lesions were found in increasing numbers as pregnancy progressed. We have not differentiated between lesions in the squamocolumnar junction area and those extending into the endocervical canal.

The per cent follow-up, 49.5 (242 of 489 patients), is certainly low. However, some of the 489 patients were recent additions to the group and time for follow-up has not yet elapsed. In others only smears were used as a method of follow-up. Only those patients with biopsy or other tissue examination after the original diagnosis was made were included in this study. For these reasons this figure probably does not accurately represent the number of patients followed or lost to follow-up.

I am unable to give you the number of patients treated by total hysterectomy after discovery of a preinvasive carcinoma in this group of patients. A high percentage, however, have had hysterectomy. Some were untreated at the time the data were tabulated. In general our policy has been to do total hysterectomy for patients with preinvasive lesions. We are not treating patients with the lesser lesions by hysterectomy but prefer to follow them. Obviously, however, such patients must be individualized in regard to treatment.

TOTAL EXCHANGEABLE SODIUM AND SPACE IN NORMAL AND PRE-ECLAMPTIC PATIENTS DETERMINED WITH SODIUM^{22}*†

Preliminary Report

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OVER the years we have been studying the changes in the body associated with pre-eclampsia-eclampsia in an endeavor to determine the cause, prevention, treatment, and possible end results. As each new study would be completed it became obvious that additional observations were necessary. Thus, serial hematocrit and serum protein studies lead to blood and plasma volume determinations,[4] then to balance studies,[5, 6] which lead to the determination of extra- and intracellular and total body water, and finally to the need for a physicochemical dissection of the body in which both physical and chemical methods are used for determining the amount of fat and lean body tissue and the water and electrolyte in each tissue and individual compartment. Since each method has errors, we have been determining the compartments by as many methods as are practical. We are in the midst of this study and hope to have it completed within the next two years. Since sodium is directly concerned with the normal as well as abnormal content of water in the body we wished to determine how much sodium is in the body, where it is located, and how long it takes for a given amount of sodium to be excreted from the body. Radiosodium^{22} was chosen rather than sodium^{24} because its long half-life of approximately 3 years, as compared with 14.8 hours for sodium^{24}, permitted us to follow its metabolism and eliminated the need for correction due to the rapid decay of Na^{24} which would have added additional errors. This report comprises some of the observations on the use of radiosodium^{22}.

Previous studies,[9, 11, 13] most of them with sodium^{24}, have shown that the time necessary for equilibration varies, in part, with the species and tissues. In the rat, the equilibration is reported by Green and associates[11] to be complete in 5 hours. The rabbit and dog require a longer period. Studies in the human indicate that equilibrium is complete after 12 hours in skin, muscle, and gastric juice but is only 90 per cent complete in cerebrospinal fluid and only 25 to 40 per cent complete in the bone[7] in 24 hours.

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Burch, Reaser, and Crondich[1] made the following observations on sodium^{24}. There was a rapid and slow rate of diffusion from the vascular bed. Fifty-eight per cent of the rapidly diffusing sodium left the plasma per minute, and 6.4 per cent of the slowly diffusing sodium left the plasma per minute. Thus, an average of 32 per cent of the total sodium in the plasma is diffused out of the vascular bed per minute and some 13 per cent of the total sodium in the interstitial fluid returned by diffusion to the plasma per minute. They calculated that for a man weighing 70 kilograms, about 4,000 Gm. of sodium per day diffuses from the vascular bed. They further speculate that if the chloride ion tends to follow the sodium ion during its diffusion there would result a diffusion of about 10,000 Gm. of NaCl out of the vascular bed per day and the return would be the same. Thus, there would be an exchange of about 50 pounds of sodium chloride back and forth through the capillary walls each 24 hours. If the rate of diffusion for water is comparable in man to the rate in animals, then about 6,300 liters of water per day diffuses out of the vascular bed and, of course, returns. They found that the sodium of the interstitial fluid of the normal subject is turned over twice as rapidly as in the patient with congestive heart failure, whereas the sodium of the plasma of the latter patient is turned over twice as rapidly as that of the normal subject. Radiosodium cannot be employed to measure an exact extracellular water volume with any degree of accuracy because a fairly large portion of the body sodium is not in the extracellular fluid. They found that the method became even more inaccurate in abnormal states characterized by edema. Some investigators have stated that the sodium space, if corrected by reducing it 20 per cent, would be comparable with the thiocyanate space.

Burch and Reaser,[2] working with sodium^{22}, made the following observations. In 4 control patients, the serum concentration of sodium^{22} had dropped to half the initial level in an average of 13.3 days (range 12-14 days). The elimination in the urine was such that one-half of the sodium^{22} would have been excreted in an average of 28.8 days (range 9 to 42 days). They noted that on an intake of 1.7 Gm. of sodium chloride the serum concentration required 25 days to reach a half value. When the sodium chloride intake was 13.7 Gm., then half the initial serum concentration was obtained in 8 days. Similar responses were noted for rates of elimination in the urine. Patients with chronic congestive heart failure who improved rapidly required an average of 20.5 days (13 to 28 days) for the serum concentration of sodium^{22} to reach one-half of the initial level and the mean rate of excretion for one-half in the urine was 29.5 days (26 to 33 days). The patients who did not improve required 27 days for the serum concentration to reduce to one-half and 60 days for the urine concentration to reduce to one-half.

Patients with the nephrotic syndrome of chronic glomerulonephritis required 56 days for the serum concentration to decrease one-half and an average of 513 days would have been necessary to eliminate one-half sodium^{22} in the urine.

They reported that one-half of the urine elimination ($U_{\frac{1}{2}}$) was greater than one-half serum concentration ($C_{\frac{1}{2}}$). This is unusual since sodium is eliminated by channels other than the urine such as sweat, tears, sputum, feces, vomitus, and other body fluids. "Binding" of sodium in cells and onto cells, proteins, and other complex molecules can account in part for these differences.

The equilibration and elimination, according to most investigators,[6-9, 11] depends largely on the sodium intake of the individual. On an average intake of 200 or more meq. of sodium per day, we found that radioactivity amounting to 10 counts above background per 20 minutes (initial counts had been 2,985) was present in the serum 14 weeks after the injection. On a sodium intake of approximately 60 to 120 meq. per day, the serum activity at the same period amounted to 83 counts per 20 minutes and the total amount of sodium injected could be accounted for more accurately. In diets containing 10 to 20 meq. of sodium the time activity lasts longer.

Lambiotte-Escoffier, Moore, and Taylor,[12] using Na^{24}, reported an increased sodium space in pre-eclamptic patients. Gray and Plentl,[10] also using Na^{24}, reported no appreciable change in sodium space or T.E.S. (39.3 [range 31.9-49.5] meq. per kilogram) in normal pregnant patients but an increase in the only patient with pre-eclampsia in their study.

Method

Radiosodium^{22} emits both gamma and beta rays and permission to use it was obtained from our University Committee on Isotopes representing the Atomic Energy Commission. We were restricted to a maximum dose of 10 microcuries in pregnant patients because of potential danger to the fetus. We found that we could use from 5 to 7 microcuries with adequate accuracy. The calculated radiation for 5 microcuries in a 60 kilogram woman amount to 54.8 milliroentgens, well below any possible danger. All procedures were approved by our Health Physics Committee and the laboratory area is examined weekly for stray radiation.

Normal nonpregnant and pregnant patients and patients with pre-eclampsia or vascular-renal disease have been restricted to the climate room which is maintained at a constant temperature of 80 degrees and a relative humidity of 45 per cent, weighed on a beam balance twice daily, given a weighed diet, and the fluid intake and output are measured. There was no visible evidence of sweating. Twelve to 18 hours after admission each patient was given intravenously known amounts of deuterium oxide, antipyrine, sodium thiocyanate, T-1824, and radiosodium^{22}. No unusual restrictions were placed on the patients other than that they must remain in the room. No sedatives, cathartics, etc., were used. Access to the adjoining cubicle for lavatory and toilet use was only under supervision of the nurse who kept the key. A limited number of patients had stool analyses and determination of the insensible weight loss.

Specimens of urine and blood were taken for control and repeated again at 15 minutes, 2, 3, 5, 7, 9, 24, and 48 hours after injection. In some cases, samples every 24 hours were continued for a longer period and a few had subsequent samples at 3 to 5 day intervals.

Two milliliters of serum was placed in a cupped nickel-plated planchet. The serum was evaporated to dryness in an oven at 100° C. and then ashed at 450° C. overnight. A small piece of filter paper was then placed in the planchet and enough water added to dissolve and distribute the ash evenly over

the base of the planchet. This water was evaporated under an infrared light and when dried the sample was ready for counting. The urine was prepared in the same way except that 4 ml. was used. A sample of the solution containing the sodium^{22} was diluted with water and assayed for the total counts injected into the patient. This was performed for each patient so that an appropriate correction could be made for the gradual decay of the sodium^{22}.

We know that the sodium space[1, 2, 14] is possibly constant for only a short time but that is true for the thiocyanate, inulin and other spaces. However, we believe changes in the sodium space, since it is a normal constituent of the body, are more significant than changes in the inulin, mannitol, etc., for these are abnormal substances and the space is determined in an abnormal method (intravenous infusion over hours or even days). We doubt the accuracy of all of these spaces in edematous subjects, and therefore are comparing the so-called sodium space for the same period of time in the same subject in the ante- and the postpartum period.

The time required for the serum concentration to reduce one-half and the urine elimination to equal one-half of the injected sodium^{22} will be given in the final report for a limited number of patients. Since many of the edematous patients had two injections within an interval of 7 to 10 days, it is obvious why the time for elimination could not be determined with any degree of accuracy.

Since equilibrium of the Na^{22} in patients ingesting normal amounts of sodium salts is very difficult to determine (we believe it possible only in patients who have been maintained for some days on an intake of sodium less than 15 meq.), the results were studied by our statistician and he advised that we use the average of the better two of the 3, 4, 5 hour periods. We know that equilibrium has not been accomplished but since we are interested in comparing ante- and postpartum values we believe our results are valid.

Calculation (example):

5 microcuries Na^{22} in 10 ml. of physiological saline solution had an activity of 23,000,000 counts per 20 minutes.

1 ml. serum had 1,200 counts per 20 minutes.

$$\frac{23{,}000{,}000}{1{,}200 \times 1{,}000} = 19.16 \text{ L. of sodium space}$$

Serum sodium was 135 meq. per liter.

Total exchangeable sodium (T.E.S.) $= 19.16 \times 135 = 2{,}587$ meq. Na.

Results

Over 170 patients have received one or more injections of sodium^{22}. Nine patients have had one or more subsequent normal babies after the initial injection, and the wife of one of the male volunteers had a normal baby following the injection of sodium^{22} into her husband. In the nonpregnant individual, one can use the weight, height, surface area, or total body water as a basis for comparison and one can repeat the injections frequently. In pregnancy, the weight and total body water are constantly increasing and the patient's postpartum weight is rarely the same as it was at the onset of pregnancy. The ideal study would be one in which all observations could be made before pregnancy and every two or three months during pregnancy and again two or three months post partum, but such observations are almost impossible to obtain. Furthermore, while pregnancy can be repeated, and we have studies in the same patient for several pregnancies, pre-eclampsia rarely, if ever, recurs. Thus, more assumptions must be made in pregnancy than in the nonpregnant

but since they are constant assumptions and since we are comparing the ante- and postpartum values on the same patient, any differences should be of value.

Normal pregnant women are compared with normal nonpregnant and with themselves after the puerperium. Pre-eclamptic and hypertensive patients are compared with normal pregnant and also with themselves after the puerperium.

We have determined Na^{23} and Na^{22} in the serum, skin, fat, muscle, edema and ascitic fluids in various types of patients and have analyzed fairly completely 8 previable live fetuses weighing between 15 to 720 grams with a time range from injection to delivery of 2 hours to 7 days and have also numerous determinations of amniotic fluid. These studies of the fetuses will be given in a separate report but, as one would expect, sodium^{22} is detectable in the living fetus within minutes after its injection into the mother. In one dead fetus at term sodium^{22} was present in the amniotic fluid in the same concentration as in the maternal serum and there was slight activity after correction for the background in ascitic fluid from the abdomen of the baby and the fetal liver. The fetal muscle, skin, and bone had no activity.

Sodium^{22} was first given to several large rabbits, and observations made as to its elimination, time required for its diffusion, and its presence in the various tissues. Fig. 1 shows that the sodium space was very constant due to the very low intake of sodium. If the sodium intake was increased, the sodium space would rapidly increase and would not return to its previous value even with a low sodium intake. The serum level of Na^{22} dropped more rapidly than could be accounted for by its excretion and would tend to rise slightly when the rabbit was again on a low sodium intake. The same changes associated with sodium intake have been noted in women subjects.

Fig. 2*A*, W. J. D., shows the sodium space and other measurements over a period of weeks in an individual who was on a limited sodium intake of 1 to 3 Gm. (50-100 meq.) a day. The sodium space remained relatively constant for about 7 days when it began to increase due to an increased intake of sodium salts. Ammonium chloride as well as the increase in the dietary sodium caused an appreciable change in the sodium space as well as in the sodium eliminated in the urine. At the end of 14 weeks a measurable amount of sodium^{22} was still present in the serum. We were able to account for all of the sodium injected with the exception of 10 per cent which we think is the approximate long-term total experimental error of the method. (Burch stated that the error was about 3 per cent, but when one considers lost or spilled urine, the error is greater.)

One-half of the serum concentration ($C_{\frac{1}{2}}$) for W. J. D. on a restricted sodium intake was reached in 20 days and for R. P. on a liberal sodium diet in 8 days. One-half the urine excretion ($U_{\frac{1}{2}}$) was accomplished in 23 and 17 days, respectively. The differences in these figures again illustrate the effect of the sodium intake on the sodium distribution and excretion.

Studies are limited in the determination of either $C_{\frac{1}{2}}$ or $U_{\frac{1}{2}}$ because patients would not remain long enough in the hospital. However, the patients were seen periodically and since they had different sodium intakes, they had different values for $C_{\frac{1}{2}}$. All had either eliminated all of the sodium^{22} or retained at a maximum only 5 per cent above the background by 70 days after the injection.

Fig. 2*B*, R. P., shows the sodium space and other measurements in a normal male who was on a sodium intake of 4 to 6 Gm. (160 to 300 meq.) per day. The sodium space rapidly increased. Ammonium chloride as well as changes in the sodium intake cause considerable alterations in the serum and urine activity. In this individual, we were able to account for only 76 per cent of

the injected sodium. Approximately 14 per cent of the sodium had not been excreted and we believe this was temporarily stored in bone where the rate of exchange is very slow.

TABLE I. ANTE- AND POSTPARTUM WEIGHTS OF PATIENTS (PER CENT)

	NORMAL		PRE-ECLAMPSIA		HYPERTENSIVE DISEASE	
KILOGRAMS	ANTE-PARTUM	POST-PARTUM	ANTE-PARTUM	POST-PARTUM	ANTE-PARTUM	POST-PARTUM
45- 49.9		14		12		4
50- 59.9	25	41	5	28		22
60- 69.9	36	28	22	36	26	26
70- 79.9	16	8	28	17	18	7
80- 89.9	16	5	33	6	7	19
90- 99.9	4		12		18	7
100-109.9		4			18	7
110-129.9	3				7	4
130-149.9					6	4
No. of patients	36		18		27	

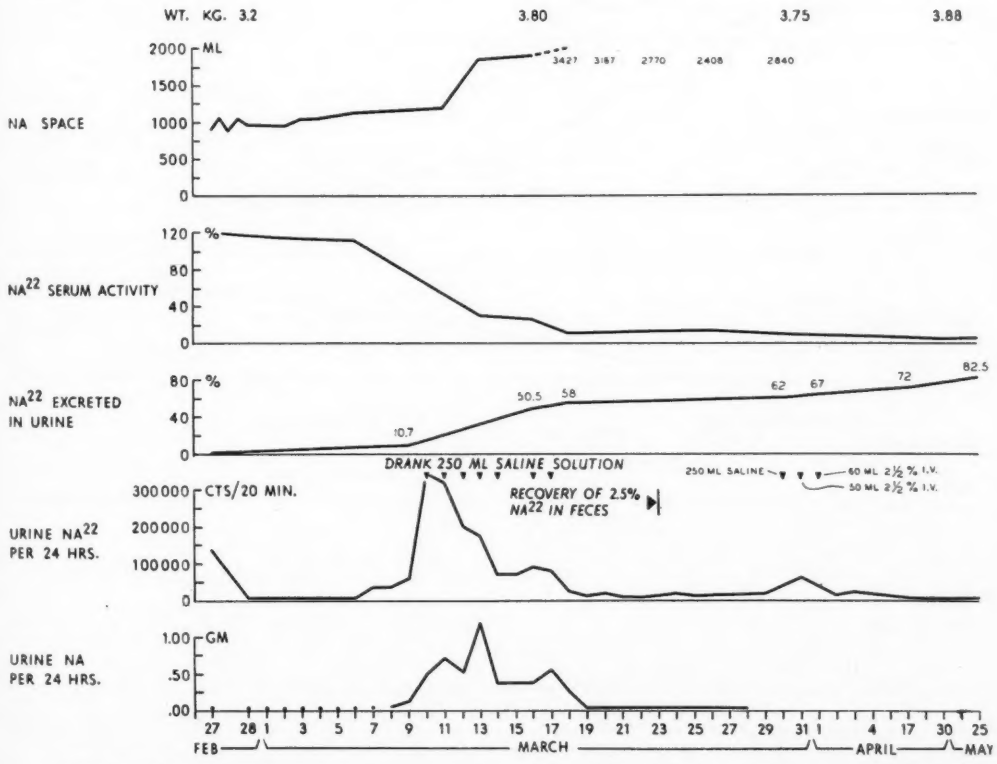


Fig. 1.—Shows the serum and urine values for sodium[23] and sodium[22] and sodium space in a rabbit. Note the constant sodium space and the marked and rapid changes due to alterations in the sodium intake.

Figs. 3*A* and 3*B* show differences in sodium space and elimination in 2 patients on identical diets and treatment for 4 to 6 days, as well as the effects on Na^{22} caused by the intravenous injections of 500-1,000 ml. of 2.5 per cent NaCl solution.

Table I shows the per cent of patients in the various groups using the maximum ante- and eighth postpartum day weights. We originally excluded

patients whose postpartum weights were over 80 kilograms, since we felt such patients were not normal, but our statistician insisted that all cases be included, in the same proportion in which they occurred in our hospital population. We also wished for a random selection but he agreed that, because of the many variables, especially if the patient refused to cooperate, we would have to use the cases at hand. It is apparent that the groups of normal and pre-eclamptic patients had essentially the same postpartum weight and the mean height was the same. The only difference was that there was a higher incidence of heavier patients in the group with antepartum pre-eclampsia, although these patients lost more weight than the normal group. The group with hypertensive disease had a much larger per cent of obese patients in both the ante- and postpartum weight groups.

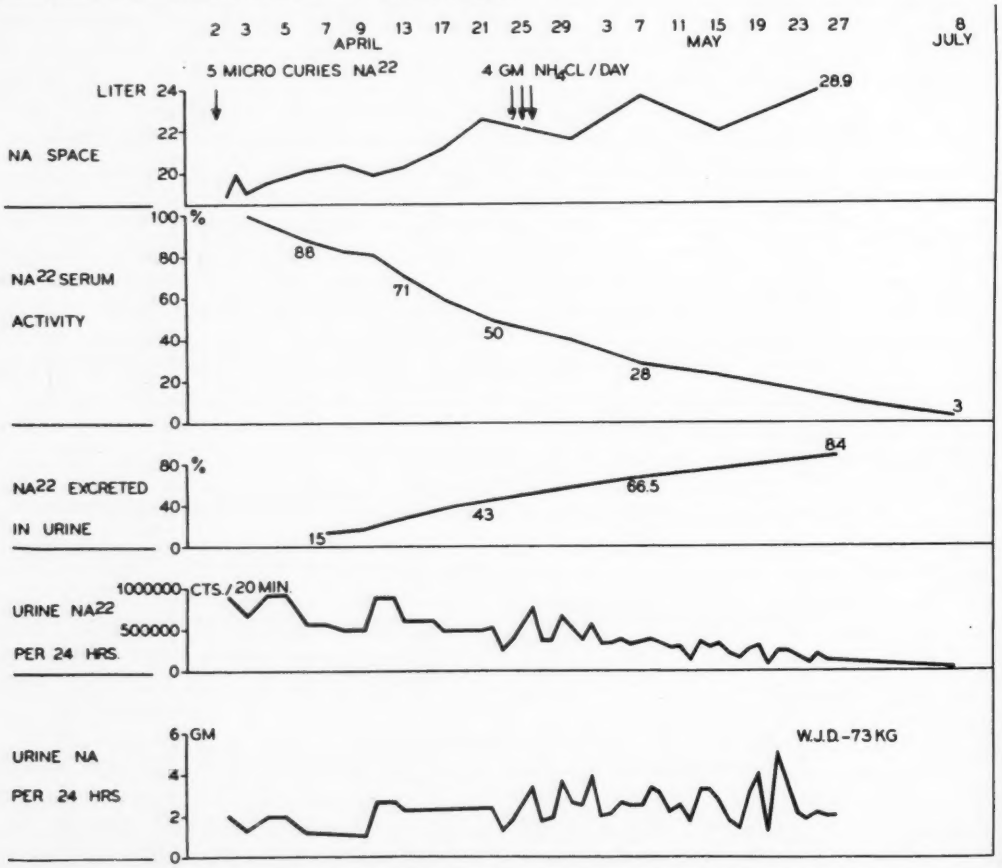


Fig. 2A.—Shows sodium space, serum, and urine content of Na^{23} and Na^{22} in normal male on sodium intake of 50 to 100 meq. (1 to 3 Gm.) as well as changes caused by ammonium chloride and increased sodium intake.

Table II shows the difference between the maximum antepartum and postpartum weights on the eighth postpartum day. We had ante- and postpartum weights as well as the weight of the baby, placenta, amniotic fluid, and blood loss on these patients but since there were varying degrees of insensible weight loss and since the weight could rarely be determined just before delivery, we concluded that the weight of the baby plus one third was the best index for the loss of body weight due to baby and items enumerated above. Thus, the corrected weight loss represents essentially the water and solutes lost from the mother's tissues during the first eight postpartum days. No corrections were

made for the small number who breast fed their babies. It is at once apparent that the pre-eclampsia group had an average water loss of 11.7 kilograms as compared with the normal group of 5.6 and the hypertension group of 9.6. The range of the corrected water losses indicates even better the tremendous water retention which had been present, especially in the pre-eclampsia group.

The average differences for corrected weights will become greater in the pre-eclampsia group and decrease in the hypertension group as the number of patients becomes larger and specially when the diagnosis of pre-eclampsia or hypertensive disease becomes more exact after another pregnancy. Hypertensive disease with abnormal weight gain and/or loss (visible or occult edema)

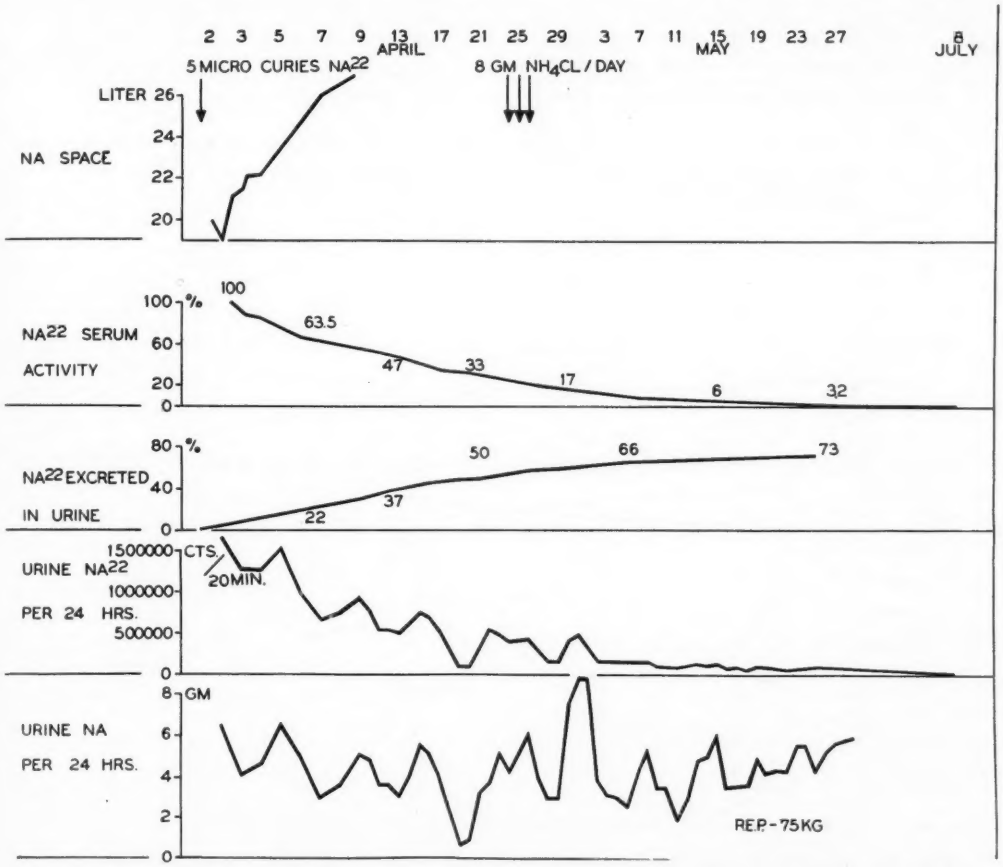


Fig. 2*B*.—Illustrates the differences in sodium space, elimination, etc., in normal male subject on sodium intake of 160 to 300 meq. (4 to 6 Gm.).

does not necessarily imply superimposed pre-eclampsia. In some of these patients 60 per cent of their weight is fat, and the latter can contain 66 per cent water (water drips if the fat is incised).

In Table III we have calculated the antepartum sodium space as per cent of the weight and the postpartum space as the per cent of postpartum weight. It is obvious that the latter, although not normal, is close to the normal values. The antepartum space tends to be normal for the weight but the number of patients with increased values is augmented and the number of patients with increased space is even higher in the pre-eclampsia group. We believe that

TABLE II. TOTAL AND CORRECTED LOSS IN WEIGHT BY EIGHTH POSTPARTUM DAY (PATIENTS PER CENT)

WEIGHT DECREASE (KILOGRAMS)	NORMAL		PRE-ECLAMPSIA		HYPERTENSIVE DISEASE	
	TOTAL	CORRECTED	TOTAL	CORRECTED	TOTAL	CORRECTED
0.1- 2.9		13				
3- 5.9	13	49				16
6- 8.9	28	35	6	35	16	40
9-11.9	46	3	18	41	24	32
12-14.9	13		34	18	48	12
15-17.9			24	6	12	
18-20.9			6			
21-22.9			12	6		
Patients, total	36		18		27	
Mean (kilograms)	10.6	5.6	15.3	11.7	11.8	9.6
Range (kilograms)	5-14	1-10	8-24	6-21	4-17	4-13

Corrected (water and solutes) = total - (weight of baby + 1/3).

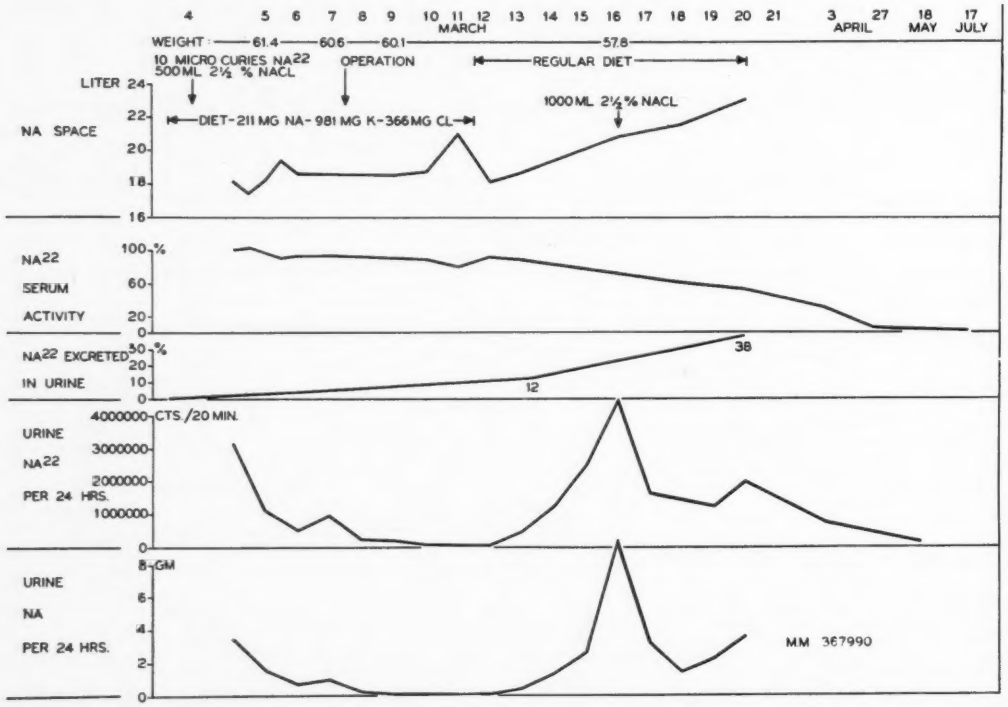


Fig. 3A.—Shows sodium space and serum and urine content of Na^{23} and Na^{22} in a patient with hypertensive disease. Note the alterations caused by intravenous injections of 500–1,000 ml. of 2.5 per cent NaCl solution as well as by regular diet. She had a hysterectomy at 22 weeks' gestation.

when these ante- and postpartum values are based on the total body water corrected for the fat, we will have some mean values and ranges which will permit a better expression of where and how water and solutes are retained.

Fig. 4 shows that when the antepartum sodium space is expressed as per cent of the postpartum weight, all pregnant patients had abnormally high spaces. This was especially true in the pre-eclampsia group. However, the hypertensive disease group, because of the high incidence of obesity, have a smaller sodium space as they also obviously have less total body water per kilogram of body weight.

TABLE III. SODIUM SPACE AS PER CENT OF BODY WEIGHT (PATIENTS PER CENT)

SPACE PER CENT	ANTEPARTUM WEIGHT			POSTPARTUM WEIGHT		
	NORMAL	PRE-ECLAMPSIA	HYPER-TENSIVE DISEASE	NORMAL	PRE-ECLAMPSIA	HYPER-TENSIVE DISEASE
16-19			4			17
20-23	4	6	21	8		23
24-27	18	17	33	25	28	
28-31	46	17	29	13	17	30
32-35	32	22	13	41	33	13
36-39		38		13	22	
40-43						
44-47						
48-51						
52-56						

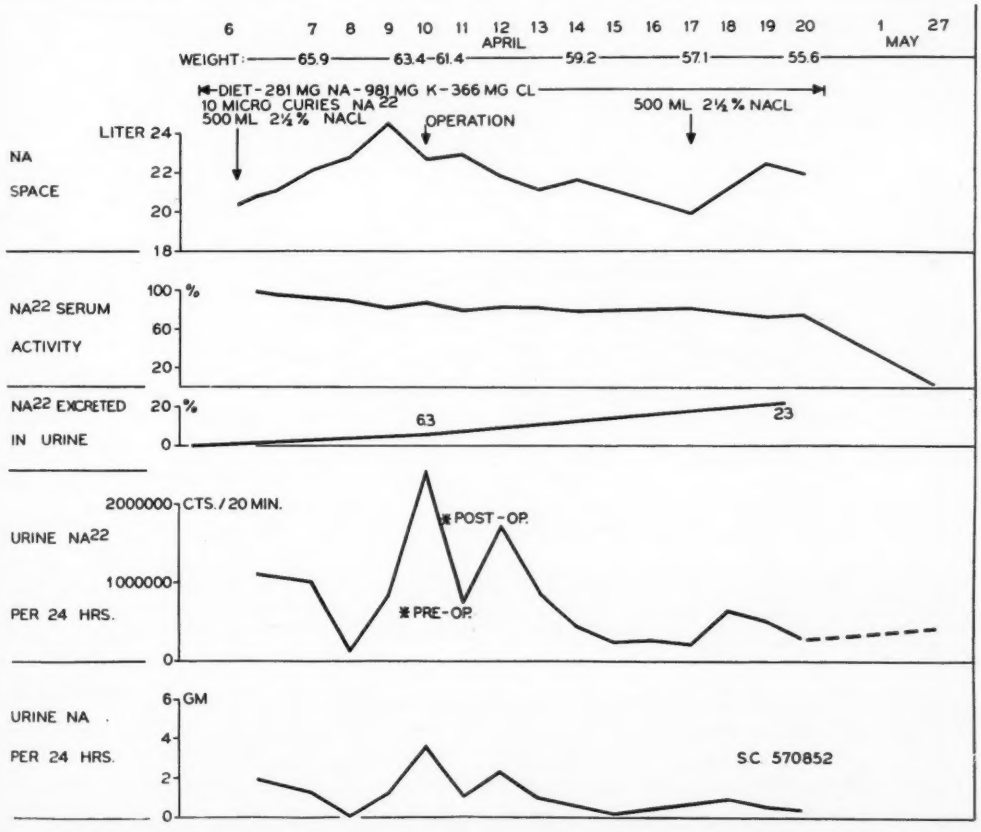


Fig. 3*B*.—Compare this patient under identical treatment with previous case. Note rapidly increasing sodium space in hypertensive patient in early pregnancy and effect of therapeutic abortion by hysterotomy on urine Na^{23} and Na^{22}.

Table IV shows the ante- and postpartum sodium space in liters for the three groups of patients. Again it is obvious that there is some increase in the sodium space in the normal pregnant patient when compared with postpartum values but not nearly as much as in the pre-eclamptic patient and, to a lesser degree, the hypertensive patient. All of these show smaller sodium spaces in the postpartum patient.

Table V shows the difference in liters between the ante- and postpartum sodium space in the various groups of patients. Again, it is obvious that there

is a much greater difference in the pre-eclamptic and to a less degree, the hypertensive group than in a normal pregnant patient, evidencing again the marked increase in water and solutes which had been present, especially in the pre-eclamptic patients.

TABLE IV. ANTE- AND POSTPARTUM SODIUM SPACE (PATIENTS PER CENT)

	NORMAL		PRE-ECLAMPSIA		HYPERTENSIVE DISEASE	
LITERS	ANTE-PARTUM	POST-PARTUM	ANTE-PARTUM	POST-PARTUM	ANTE-PARTUM	POST-PARTUM
12-15.9	3	24		11	4	19
16-19.9	45	52	11	50	22	31
20-23.9	39	24	38	28	35	31
24-27.9	10		28	11	26	19
28-31-9	3		6		9	
32-35.9			17		4	

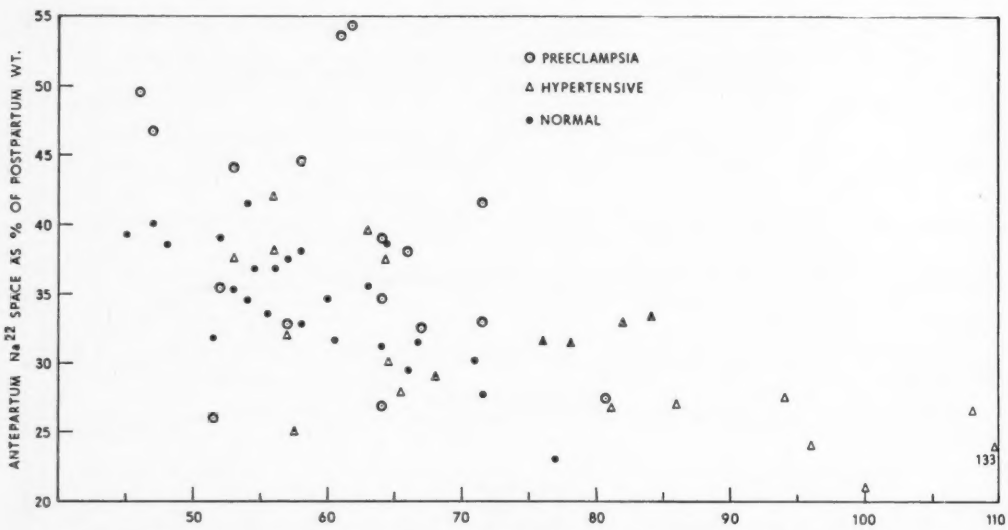


Fig. 4.—The antepartum sodium space is expressed as per cent of the postpartum weight. All pregnant patients had higher than normal spaces with this method of expression but this was particularly marked in the pre-eclamptic group. The patients with hypertensive disease, because of the high incidence of obesity, had a relatively smaller sodium space. The abscissa is kilograms of body weight.

Table VI shows the averages, the ranges, and the differences in milliequivalents as well as per cent of change for the total exchangeable sodium (T.E.S.) for ante- and postpartum determinations. The pre-eclamptic patient, although her average weight was less than that of the hypertensive patient, had a much higher T.E.S. in the antepartum period and showed a 32 per cent decrease by the eighth postpartum day . The decrease in the groups of normal and hypertensive patients was 10.8 and 5.2 per cent, respectively. The importance of determining fat is again illustrated by the fact that the heavier type of patient with hypertensive disease had proportionately less T.E.S. at term than the normal pregnant patient. The average value in the postpartum period was higher than that of the normal postpartum patient but when calculated on a per kilogram basis there were fewer milliequivalents per kilogram in the hypertensive group due to the fat.

Table VII shows the milliequivalents of T.E.S. per kilogram of body weight for both ante- and postpartum patients. It is worth noting that there is some regulating mechanism which tends to keep the T.E.S. constant for the body

weight. There is more than the normal amount in the pre-eclamptic antepartum patient than in the normal pregnant woman. The hypertensive patient, because of her obesity, shows a lower T.E.S. per kilogram of body weight both ante partum and post partum. Both normal and hypertensive patients showed an increase in the postpartum value but the pre-eclamptic patients had a decrease. Here again is a demonstration of a basic disturbance in water and sodium ions in pre-eclampsia, noted by us in several previous reports.

TABLE V. DIFFERENCE BETWEEN ANTE- AND POSTPARTUM SODIUM SPACE (PATIENTS PER CENT)

DIFFERENCE (LITERS)	NORMAL	PRE-ECLAMPSIA	HYPERTENSIVE DISEASE
1- 1.9	29	6	23
2- 2.9	35	6	8
3- 3.9	6	12	23
4- 4.9	18	12	15
5- 5.9		28	15
6- 6.9	12		8
7- 7.9		18	8
10-10.9		6	
12-12.9		6	
13-13.9		6	

TABLE VI. TOTAL EXCHANGEABLE SODIUM IN ANTE- AND POSTPARTUM PATIENTS (AVERAGE, RANGE, AND DIFFERENCE)

	NORMAL PREGNANCY		PRE-ECLAMPSIA		HYPERTENSIVE DISEASE	
	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
Antepartum	2,776	2,394-3,554	3,456	2,820-4,701	3,213	2,600-4,245
Postpartum	2,505	1,883-2,936	2,639	2,639-3,684	3,007	2,488-3,660
Difference	271		817		206	
Change %	-10.8		-31.8		-5.2	

TABLE VII. MILLIEQUIVALENTS PER KILOGRAM OF EXCHANGEABLE SODIUM IN ANTE- AND POSTPARTUM PATIENTS (AVERAGE, RANGE, AND DIFFERENCE)

	NORMAL PREGNANCY		PRE-ECLAMPSIA		HYPERTENSIVE DISEASE	
	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
Antepartum	40.2	27.9-45.5	44.9	31.2-53.0	35.9	28.5-43.7
Antepartum Postpartum weight	47.3	31.2-53.0	56.7	37.5-73.9	42.1	31.9-52.3
Postpartum	42.3	30.0-53.9	42.8	33-2-52.0	37.6	27.5-44.4
Difference	+2.3		-2.1		+1.7	

TABLE VIII. AVERAGE VALUES FOR SODIUM SPACE BASED ON WEIGHT, HEIGHT, AND SURFACE AREA

SODIUM SPACE	NORMAL PREGNANCY	PRE-ECLAMPSIA	HYPERTENSIVE DISEASE
Milligrams per Kilogram.—			
Ante partum	343.0	361.0	312.0
Post partum	300.0	255.0	245.0
Milligrams per Centimeter Height.—			
Ante partum	125.0	150.0	143.0
Post partum	110.0	125.0	127.0
Liters per Square Meter.—			
Ante partum	11.8	13.3	12.2
Post partum	11.1	12.3	11.0

Table VIII shows the average values for the sodium space based on weight, height, and surface area. Differences are evident. The effect of fat is seen in the hypertensive group. Pre-eclamptic patients, although clinical edema has disappeared, still have an enlarged sodium space. These values are tentative for the number of cases is small.

Comments

Radiosodium[22] as the chloride salt, when injected intravenously, diffuses rapidly in the body but it is difficult to determine when equilibrium has been reached. This is due to the fact that the rate of diffusion is slower in some tissues, notably bone. Furthermore, the sodium content of the patient's diet directly influences the rate of diffusion. The individual who has been on an intake of 4 or more Gm. of sodium salts per day has a considerable store of sodium ions in the body, a portion of which is presumably in bone[7] with a very slow rate of diffusion. One fact must be kept in mind, namely, sodium is found in almost every tissue or cell in the body in varying concentrations. Since the amount and concentration of all salts in the body are dependent on each other it has been obvious to most investigators for several years that blood analyses and even balance studies were insufficient in studying normal and abnormal changes in the body. The body consists of bone, soft tissue, and fat, in each of which certain salts are predominant. Each tissue has an extra- and an intracellular compartment. Thus, the possible ramifications become increasingly difficult to determine and to interpret. The compartments concerned are extra- (plasma and interstitial volume) and intracellular fluid (cells of muscles, organs, bone, etc.). In addition there is an extracellular compartment (connective tissue) of muscles, organs, and fat. Since fat can comprise over 60 per cent of the body weight and since the connective tissue of the excised fat from the edematous abdominal wall can contain 66 per cent water (actually drips water from cut surface) and 90 meq. of sodium per kilogram of wet tissue as compared with 7 per cent water and 6 meq. of sodium in normal fat, it is obvious that there is a potentially large extracellular space for sodium chloride diffusion in the obese individual. It appears that although the diffusion rate is presumably normal in this connective tissue of fat, yet the space seems to act like the expansion tank on the old type of hot water heating system (only overflowing when the water boiled), that is, comparatively speaking, excess fluid and electrolyte cause effects on the cardiovascular-renal physiology only under extreme conditions. Thus, a rapid gain of 3 kilograms in a 70 kilogram patient with 20 per cent body fat would presumably affect the intracellular fluid and body physiology to a greater degree than the same gain in a 70 kilogram patient with 40 per cent fat.

The total exchangeable sodium is also increased but when it is calculated on a per kilogram basis there is some indication that the water retention in pregnancy and hypertensive disease is greater than the sodium retention, as indicated by an increase in the milliequivalents of sodium per kilogram by the eighth postpartum day. The effect of fat is evident in the hypertensive disease group where the milliequivalents of exchangeable sodium per kilogram of body

weight are lower than the normal in both ante- and postpartum studies. We believe that when our studies are completed we will find significant changes in the exchangeable sodium and water when values are based on the total body water of the lean body mass.

Normal adult subjects in a properly controlled environment can remain in sodium balance on approximately 10 meq. of sodium per day. However, since everyone ingests 100 or more meq. of sodium per day, it is obvious that the body over the ages has developed certain defense mechanisms to handle excess sodium salts.

Normal pregnant and nonpregnant women have an inherent error in electrolyte studies because all have been on a diet containing sodium, potassium, chloride, and other anions and cations far in excess of the normal requirements for balance. Since the kidney is very sensitive in its excretion or retention of electrolyte and water in response to the hormones of the posterior pituitary and adrenal glands, it is obvious that normal adults can remain in sodium balance on diets ranging from 10 to 600 meq. (0.23-14.0 Gm.) of sodium per day. Analyses of a 24 hour urine specimen from almost any normal subject shows a large excess of the various ions needlessly ingested. The excess ingestion of these various electrolytes has necessitated certain changes in the body and we raise the question as to the possibility that the histology and function of the cortex of the adrenal gland and perhaps the posterior pituitary gland, and certain cells in the kidney associated with sodium excretion or retention now thought to be normal are actually abnormal.

We have a few patients with a past history of severe vascular-renal disease who were sufficiently interested in themselves to remain on a low sodium and potassium diet for the 20 weeks before delivery, with the result that they did not gain or gained only 1 to 2 kilograms and the weight loss at delivery was 6 to 8 kilograms. These patients had no edema of the ankles at any time and much less increase in the plasma and blood volume than usual. Their faces never showed the slight fullness usually found in late pregnancy. Our studies seem to indicate that if nonpregnant and pregnant women were constantly on a normal sodium (approximately 10 meq.) and potassium (approximately 50 meq.) intake with a ratio of sodium to potassium of 1 to 4 or 5, their course would be as described above and pre-eclampsia would rarely, if ever, occur.

It is now fairly generally known that there is no single change in a body compartment or space, that is, an increase in plasma volume is not limited just to the circulation but involves a change in the interstitial fluid as well as the intracellular fluid. It is also fairly well known that the body attempts to maintain a constant homeostasis and undoubtedly has areas where excess electrolyte and water may be stored with the least effect on the general physiology. This is borne out by some experiments by Smirk,[15] who showed that, when water was ingested, the major portion was deposited in the leg and thigh and then slowly reabsorbed and excreted over a period of 3 hours.

Summary

Radiosodium^{22} with a half-life of 3 years is the ideal substance for determining the amount of sodium in the body and its elimination. The equilibration for sodium^{22} as determined by the serum concentration and the total amount remaining in the body depends upon the sodium intake for the preceding period and days following the injection. The sodium space in patients who are ingesting 4 or more Gm. of sodium salts per day probably never reaches equilibrium.

In the patient on a sodium intake of 4 or more Gm. per 24 hours, the radioactive sodium is no longer detectable by 14 weeks but in the patient on a sodium intake of less than 2 grams per 24 hours, the sodium was still determinable at the end of 18 weeks, and with a still smaller intake of sodium the turnover was still slower, reaching approximately 22 weeks.

In the normal subject on an average or high intake of sodium chloride, although the turnover is more rapid, approximately 13 per cent of the injected sodium^{22} at the end of 14 weeks is still unaccounted for and is probably stored in bone.

A basis for comparing values between pregnant patients is extremely difficult, and will probably have to be based upon the total body water in the lean body mass.

The sodium space is increased in normal pregnancy and markedly increased in pre-eclamptic patients and to a lesser degree in the hypertensive disease group. This is true whether one calculates it as the total sodium space, as the milliliters per kilogram, per centimeter of height, or per square meter of body surface.

The total exchangeable sodium is increased approximately 10 per cent in the normal pregnant patient and is markedly increased in the pre-eclamptic patient as evidenced by a 32 per cent drop by the eighth postpartum day.

The hypertensive disease group is characterized by a larger amount of total exchangeable sodium but if calculated on a per kilogram basis then the values are less than normal, indicating that fat does not contain as much water and electrolyte as does the lean body tissue.

References

1. Burch, G., Reaser, P., and Crondich, J.: J. Lab. & Clin. Med. **32**: 1169, 1947.
2. Burch, G., and Reaser, P.: J. Lab. & Clin. Med. **34**: 1, 1949.
3. Cheek, D., and West, C.: J. Clin. Invest. **35**: 763, 1956.
4. Dieckmann, Wm. J.: Am. J. Obst. & Gynec. **32**: 927, 1936.
5. Dieckmann, Wm. J., and Pottinger, R. E.: Am. J. Obst. & Gynec. **70**: 822, 1955.
6. Dieckmann, Wm. J., and Pottinger, R. E.: Am. J. Obst. & Gynec. **71**: 596, 1956.
7. Edelman, I., James, A., Baden, H., and Moore, E.: J. Clin. Invest. **33**: 122, 1954.
8. Farber, Saul J., and Soberman, R.: J. Clin. Invest. **35**: 779, 1956.
9. Forbes, G., and Perley, A.: J. Clin. Invest. **30**: 558, 1951.
10. Gray, M. J., and Plentl, A. A.: J. Clin. Invest. **33**: 347, 1954.
11. Green, D. M., Reynolds, T. B., and Girerd, R. J.: Circulation Res. **3**: 330, 1955.
12. Lambiotte-Escoffer, C., Moore, D. B., and Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **66**: 18, 1953.
13. Miller, H., and Wilson, G.: Clin. Sc. **12**: 97, 1953.
14. Warner, G. G., Sweet, N. J., and Dobson, E. L.: Circulation Res. **1**: 486, 1953.
15. Smirk, F.: J. Physiol. **78**: 113, 127, 147, 1933.

Discussion

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—We have been fortunate this year in having two papers on the program dealing with the biochemistry of human reproduction, both by accomplished investigators. One, of course, was Dr. Page's presentation of yesterday morning. The other is the present paper by Dr. Dieckmann. Even casual audition of these two reports must have impressed the listener with the complexity of the subject matter reviewed, the intricacy of the methods used and, more important, with the years of biochemical study and application which must have been necessary to master and interpret the techniques employed. Yet this is the direction which basic research in obstetrics is clearly taking. We are hearing more and more, as time goes on, about isotopes, the Donnan equilibrium, oxygen gradients across the placenta, dissociation curves, fetal hemoglobin, enzyme systems, ionic pumps and even more recondite topics. This is well and good because the day has passed when the basic principles of placental transfer, water balance, and the like can be studied effectively by rudimentary methods.

And why do I mention this here? Because every member of this Society is engaged in one way or another with the training of young men, some of whom may be interested in pursuing an academic career in obstetrics and gynecology. And today any young man so interested should understand that, to attain distinction in academic obstetrics and gynecology, he must not only acquire clinical excellence but must gain mastery of—not mere cookbook knowledge of—but mastery of some basic discipline. In this connection let it be noted also that the broad fields covered by Dr. Page's and Dr. Dieckmann's papers make up a fairyland of research unsurpassed in any other specialty. And, if properly presented, the problems involved can constitute a challenge, an appeal, and an inspiration to young men of inquiring mind everywhere. As we endeavor to attract such superior young men to our specialty, let us not forget the potentialities of this drawing card.

Dr. Dieckmann's paper, which shows that the sodium space is increased even in normal pregnancy, is timely because another recent study in which similar techniques were used showed no such increase. That investigation, however, was based on only 9 cases and, in view of the wide range of values obtained by Dr. Dieckmann in different individuals, it appears that a sampling error was responsible for the discordant findings reported in the other study. In 1943, Chesley reported measurements of the thiocyanate space in 442 gravidas at different times in pregnancy, ranging from the eighth to the fortieth week. Although the thiocyanate space is not the same as the sodium space, it is believed, like the sodium space, to be a rough index of extracellular water. Chesley found that the total increase in size of the thiocyanate space in pregnancy was 6.3 L., of which only 1.5 to 2.0 L. could be allocated to the products of conception.

The great importance of Dr. Dieckmann's paper lies not only in the circumstance that his series is large enough to avoid sampling error, but in the fact that he has investigated the behavior of the actual substance whose augmentation in the interstitial spaces is believed to be responsible for the edema of normal pregnancy and for the more pronounced edema of pre-eclampsia. In so doing he has shown that the fluid-filled spaces of the body available for the solution of sodium are increased in volume as gestation advances. This is another and perhaps more graphic way of saying that pregnancy is associated with an increased retention of sodium (especially in pre-eclampsia), a circumstance which has previously been demonstrated by sodium balance studies. But, if the edema of normal pregnancy and pre-eclampsia is attributable to sodium retention, why does this ion tend to be retained? Why is the sodium space enlarged? This, of course, is one of the great enigmas of obstetrics. With his rich background in both clinical and research fields, it is to be hoped that Dr. Dieckmann will be able before long to elucidate this enigma in the same meticulous and convincing fashion as he has already clarified so many other basic problems in the toxemias of pregnancy.

DR. FRANK E. WHITACRE, Nashville, Tenn.—I am indebted to Dr. Howard Morgan of the Department of Obstetrics and Gynecology of Vanderbilt University School of Medicine for material aid in this discussion. The excessive accumulation of sodium in the pre-eclamptic patient has been demonstrated by the use of sodium^{22}. The location of this sodium within the body water and the kinetics of its excretion remain to be reported. The relationship between dietary intake of sodium and the rate of its excretion is impressive, but will make the interpretation of data from toxemic patients with widely varying sodium intakes difficult to evaluate. Data concerning the thiocyanate space determinations that were done would be helpful in localizing this sodium to the correct body compartment.

Current methods have shown the plasma volume to expand in normal pregnancy by 25 to 50 per cent. The level of serum sodium is decreased. The toxemic patient, however, frequently has a plasma volume similar to that of the nonpregnant woman. Whatever increase there may be in extracellular volume occurs in the interstitial fluid. Using antipyrine and inulin, Lambiotte-Escoffier and associates have found that a portion of the fluid retained in toxemia is intracellular.

In a previous report, Dr. Dieckmann presented data concerning the sodium and potassium content of muscle and skin in toxemic patients. Although the muscle sodium was increased in normal pregnancy, a decrease was found in pre-eclampsia and hypertensive disease. Data were lacking concerning its distribution between intracellular and extracellular water. The analyses favor an interpretation of no increase in intracellular sodium.

Careful studies of the electrolyte balance of the postoperative period have shown interesting corollaries to the data here. Again there is sodium retention accompanied by an increase in extracellular volume. The aldosterone excretion of the postoperative patient has been found to be increased, as has the aldosterone excretion of patients with toxemia. A reasonable cause-and-effect relationship is possible between the excretion of this hormone and the observed sodium retention.

As Dr. Dieckmann has emphasized in the past, no known diuretic or mode of therapy for pre-eclampsia will produce sodium diuresis in established toxemia. Only delivery is curative. Recently a new mode of therapy has been suggested—to decrease aldosterone excretion by drug therapy. Amphenone has been shown to have this effect in medical patients. This compound and also competitive inhibitors of aldosterone action appear to be the next step in therapy, and one which offers a good possibility of correcting the abnormal sodium retention associated with this syndrome.

DR. RUSSELL R. DE ALVAREZ, Seattle, Wash.—With the statement that sodium space is increased in normal pregnancy I agree, on the basis of work which we are doing serially on the same patient in the same pregnancy at monthly intervals throughout the pregnancy, 3 days after delivery, and 6 weeks post partum. The question is, Why is the sodium retained? Perhaps I have heretofore believed everything I have read, and such reading repeatedly states that the glomerular filtration rates during normal pregnancy throughout pregnancy are elevated from their normal of 120 c.c. per minute to 180 c.c. per minute. Most such reports are based upon scattered determinations on many patients during pregnancy, so that the curve has not been clearly determined for the same patient during pregnancy. Because these determinations are trying experiences for patients, most normal pregnant patients are reluctant to undergo the necessary studies for the sake of science alone. On our serial determinations we cannot agree with the so-called "standard" observations. We find a progressive decrease in the glomerular filtration rate, even though it is high at the eighth to tenth week of pregnancy, reaching levels of 160 to 180 c.c. per minute, but continuously decreasing to levels approaching 100 c.c. per minute. If this is true—and this is the way we find it in the patients whom we followed—then there is made the perfect setting for increased tubular reabsorption, not only of water but of sodium, which would then set the field for an increase in the sodium space and the logical increase for development of toxemia. Then all normal pregnant patients could possibly be classified as developing some degree of pre-eclampsia, if you will. Similarly, we have found that, as pregnancy advances, the renal blood

flow or renal plasma flow is decreased. We would therefore expect a change in the serum sodium values of these patients. Yet I cannot concur in the statement that was made here and other statements made previously that there is a decrease in the serum sodium during normal pregnancy. In the postpartum period a marked increase in the glomerular filtration rate occurs; possibly this may account for the diuresis and pass for what is called lowered renal threshold. Closer attention to and a better understanding of some of the physiologic processes and mechanisms with simultaneous correlation of all these factors dealing with filtration, renal blood flow, sodium reabsorption, excretion, distribution, and total body water will permit clearer analysis of the basic features responsible for the development of toxemia of pregnancy.

DR. DIECKMANN (Closing).—The discussants' comments are worth while but they did not help me with any suggestions. Our results on serum sodium in patients with toxemia of pregnancy are similar to those of Dr. de Alvarez. We have no low serum sodium values unless the patient has been given an excessive amount of 5 per cent dextrose solution while oliguric or has been vomiting.

We are using the water method for determining the specific gravity and obtained a value of 1.053 on Captain B.; with the helium method in his laboratory the specific gravity was 1.048.

The following data illustrate a partial physiochemical analysis of one pregnant patient, P. M.:

	27 WEEKS	35 WEEKS	7 WEEKS POST PARTUM
Weight (kilograms)	60.99	64.2	56.09
Density	1.037	1.033	1.034
Fat %	28.0	29.0	29.0
Lean body weight (kilograms)	43.92	45.58	39.82
Total body water (liters)	34.27	35.99	32.00
Extracellular water (liters)	18.86	19.23	16.33
Intracellular water (liters)	15.41	16.76	15.67
Sodium space (liters)	17.4	19.52	14.51
Total exchangeable sodium (meq.)	2,384	2,674	2,002

HEMOPHILUS VAGINALIS VAGINITIS*†

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A TYPE of vaginitis produced by a previously unrecognized bacterium was reported by Gardner and Dukes[1] in 1955. They described the clinical aspects, the appearance of the organism in wet mount, Gram stain, and culture, some of the biochemical properties of the bacterium, and its pathogenicity. To it they assigned the name *Hemophilus vaginalis.*

In 1953, Leopold,[2] whose work was unknown to Gardner and Dukes, described a similar or possibly identical organism which he isolated from the urethra of males and the cervices of women, and stated that its growth requirements and morphology suggested a close relationship to the genus Hemophilus.

In rather quick procession several reports have appeared which substantiate the existence of this bacterium and seem to confirm the evidence that this organism can produce leukorrhea and vaginitis.[3-7]

Amies and Jones[7] called attention to the fact that a bacterium designated as *Hemophilus influenzae* was isolated from the female genital tract in 1936 by Thompson[8] and from the genitourinary tract in 1947 by Henriksen.[9]

The work reported here was undertaken with two points of view in mind, namely, to attempt to isolate the bacterium according to the method of Gardner and Dukes,[1] and second, to evaluate its relationship to leukorrhea.

Material and Methods

The material consisted of 211 private gynecologic patients, aged 20 to 63 years, all of whom complained of leukorrhea. The investigation was conducted with the use of wet mounts, Gram stain preparations, and cultures. *H. vaginalis* was isolated in 89 (42.2 per cent) of the 211 patients with leukorrhea.

Cultivation of the *H. vaginalis* organism was carried out as closely as possible in the manner stipulated by Gardner and Dukes.[1]

Due to the collection of specimen material from private patients, the following experimental regimen was instituted. Specimens collected in the office were placed into a sterile tube, and then immediately transferred to Casman's[10] blood agar plates, thioglycolate and nutrient broth. Slide preparations were made for Gram staining procedure. The blood agar plates were properly

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streaked and placed within a CO_2 candle jar. All cultures were incubated at 37° C. for 24 hours in the office laboratory. A wet mount of the specimen material was examined immediately under the microscope and the remainder of the wet specimen material was placed in the ice chest. Twenty-four hours later all cultures, specimens, and slides were removed from the office laboratory and transferred to the laboratory at Northwestern University Medical School.

A second wet mount was prepared, Gram stains were performed, and cultures were examined for the presence of *H. vaginalis* in the laboratory. Colonies upon solid culture media were examined with the aid of a dissecting microscope. Colonies of typical colonial morphology were noted, picked, and transferred to a series of solid and liquid media for isolation and determination of sensitivity to a variety of antimicrobial agents. The latter was accomplished with the aid of B. B. L. Sensi-discs. All cultures were prepared in duplicate and incubated at 37° C. at atmospheric and increased CO_2 tension (candle jar).

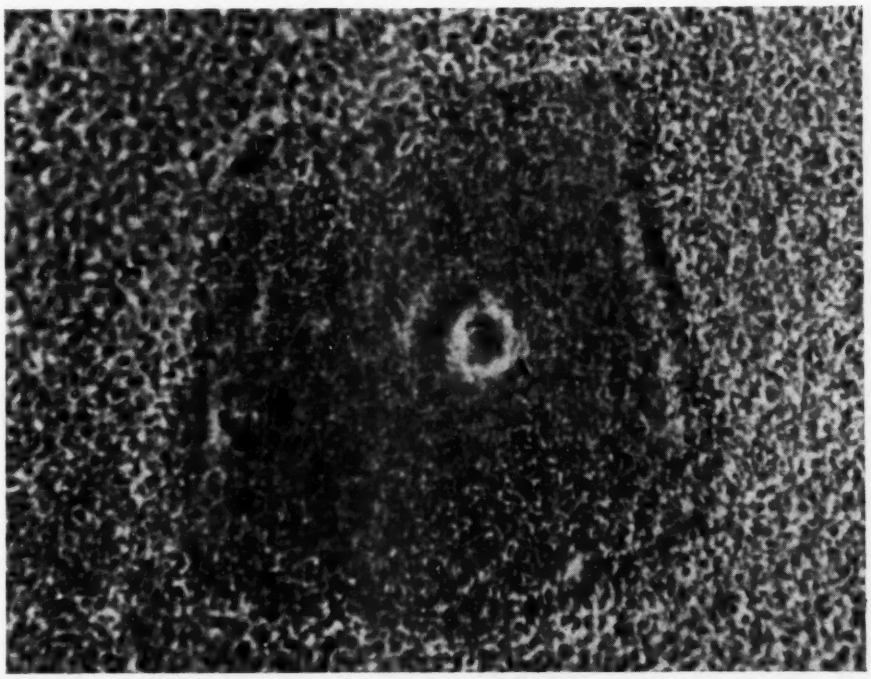


Fig. 1.—Photomicrograph (phase microscope) of a wet-mount preparation showing a large squamous epithelial cell in a dense mass of *Hemophilus vaginalis* organisms. These organisms completely cover the surface of the cell and obliterate its cell membrane. This is a "clue cell" (Gardner and Dukes). In this specimen there is a complete absence of leukocytes despite the myriads of *Hemophilus vaginalis*.

The criteria for a positive diagnosis of *H. vaginalis*[1] were based upon: (1) positive "clue cell" in the wet mount; (2) the presence of typical small gram-negative bacillary forms somewhat pleomorphic on Gram stain; and/or (3) the typical appearance of the colonies on culture and the demonstration of gram-negative pleomorphic rods in these colonies. Smooth "dew drop" pin-point colonies on Casman's blood agar medium containing 5 per cent defibrinated rabbit blood are typical of *H. vaginalis*. A dissecting microscope with oblique lighting directed upon the surface of the culture plate was utilized to detect these pin-point colonies.

Pertinent clinical data were recorded on records specifically prepared for the purpose. Subjective symptoms and objective findings including redness of the vulva and vagina, amount, color, frothiness, consistency, and odor of the discharge, condition of the cervix, if present, and pH of the vaginal mucosa at a point near the vault lateral to the cervix were noted. Follow-up studies were conducted at intervals of one to 2 months during the one and one-half years consumed in this investigation.

Results

Microbiologic Aspects.—

Wet mount: One of the criteria for a positive diagnosis of the presence of *H. vaginalis* was the "clue cell" described by Gardner and Dukes. Such "clue cells" observed on thin preparations under a cover slip with oil immersion lens are epithelial cells with a massive accumulation of *H. vaginalis* organisms on the cell surface and surrounding the cell (Fig. 1). The clarity of the cell wall is obliterated and the nucleus of the epithelial cell is peculiarly refractile. This nonmotile bacterium, usually in vast numbers, is predominant in the field between the epithelial cells and tends to render inconspicuous the other bacteria that are present.

Another striking feature is the paucity of leukocytes. In 28 of the vaginal specimens from 47 patients there were no leukocytes, in 10 there were a few, in 4 there were a moderate number, and in 5 the leukocytes were abundant. Their scarcity was noted by Gardner and Dukes, Wurch and Lutz,[3] and Deming.[4] Ray and Maughan[6] reported few leukocytes in 42 and many in 24 specimens obtained from 66 patients with leukorrhea. Amies and Jones[7] found leukocytes to be rather abundant in all their smears studied. The significance of the sparsity of leukocytes in patients with *H. vaginalis* vaginitis is unknown but it is a rather typical finding and is in marked contrast to the numerous leukocytes accompanying other types of vaginitis.

As one becomes acquainted with the appearance of wet-mount preparations, the accuracy of diagnosis by this means is quite high. It was correctly made by this method in 82 of the 89 patients. Gram stain preparations were correct in 85 of the 89. Cultures were positive in 79.

Gram stained direct smears: The bacteria, in diffuse and/or localized masses often filling the field, are small, pleomorphic, gram-negative bacilli measuring 0.3 μ-0.5 μ in width by 0.6 to 1.6 μ in length. Morphologically, the thin straight or slightly curved bacilli and the coccobacillary forms were accepted as *H. vaginalis.* Occasionally long filamentous streptobacillary forms were encountered which we did not identify further and did not include in this study as *H. vaginalis.* The *H. vaginalis* organisms consistently assume a striking but vague and indescribable pattern which makes differentiation from small pleomorphic gram-negative staining diphtheroids difficult.

Culture: Upon Casman's[10] blood agar with 5 per cent defibrinated rabbit blood incubated at 37° C. under increased CO_2 tension, *H. vaginalis* produced circular, convex, pin-point, "dew drop" colonies. These colonies were readily detected from other bacterial colony forms, in the majority of instances, with the use of the dissecting microscope and oblique lighting. Such colonies were picked and when stained by Gram's method revealed small gram-negative pleomorphic bacillary types.

Growth in liquid medium such as thioglycolate broth did not afford the same degree of perfection in identifying *H. vaginalis,* owing to the abundant overgrowth of other bacteria generally present in the sample material. The typical "puff ball" appearance of *H. vaginalis*[1] growing in thioglycolate broth was rarely seen.

Cultivation of patient material resulted in successful isolation of so-called *H. vaginalis* as described by Gardner and Dukes. However, their observation that such organisms invariably appeared in pure culture form was only rarely seen by us. Pleomorphism and variability of staining reaction were frequently encountered. Casman's and thioglycolate media did not lend themselves to prolonged maintenance of viable cultures nor the ability to maintain viable cultures upon more than three or four subcultures.

TABLE I. BACTERIAL SENSITIVITY STUDIES

	OUR RESULTS			AMIES AND JONES RESULTS		
DRUG	CONCENTRATION	SENSITIVE	RESISTANT	CONCENTRATION	SENSITIVE	RESISTANT
Penicillin	2.0 units	7	2	1.0 unit	13	
				100 units		10
Streptomycin	10.0 mcg.	3	2	4 mcg.	22	1
Tetracycline group	----	--	--	10 mcg.	23	0
Terramycin	5.0 mcg.	63	9	----	--	--
Aureomycin	5.0 mcg.	7	2	----	--	--
Tetracycline	5.0 mcg.	6	1	----	--	--
Chloromycetin	5.0 mcg.	9	0	8.0 mcg.	23	0
Novobiocin	----	--	--	2.0 mcg.	14	7
Erythromycin	2.0 mcg.	8	1	1.0 mcg.	23	0
Bacitracin	2.0 units	41	5			
Tyrothricin	0.2 mg.	37	23			
Tyrothricin with protamine	0.2 mg. 0.8 mg.	20	4			
Protamine	0.8 mg.	9	15			
Vagisol	1.0 mg.	3	14			
Polymyxin B	5.0 mcg.	1	3			
Triple Sulfa	0.25 mg.	8	2			
Sulfanilamide	0.25 mg.	7	1			
Neomycin	5.0 mcg.	6	3			
Carbomycin	2.0 mcg.	2	2			

Sensitivity studies: Sensitivity of *H. vaginalis* isolated from a number of patients to several antibiotics is given in Table I. Though the number of strains tested under all circumstances was not large, for all drugs tested against *H. vaginalis* good agreement occurred between our results and those of Amies and Jones.[7]

Clinical Aspects.—

In the 211 patients with leukorrhea, *H. vaginalis* was identified in 89. Accurate evaluation of the relationship of this bacterium to leukorrhea necessitated the exclusion of patients in whom either trichomonads or *Candida albicans* coexisted with *H. vaginalis,* since the presence of either would make it hazardous to draw conclusions concerning the significance of *H. vaginalis* alone.

Patients with *H. vaginalis* (without Trichomonas or Candida)	59	66.3%
Patients with *H. vaginalis* and Trichomonas simultaneously	21	23.6%
Patients with *H. vaginalis* and Candida simultaneously	6	6.7%
Patients with *H. vaginalis,* Trichomonas, and Candida simultaneously	3	3.4%
Total	89	100.0%

The number of 59 patients having *H. vaginalis* alone was further reduced because 7 patients did not have follow-up studies and 5 patients acquired

either trichomonads or Candida in the flora at the precise time the *H. vaginalis* disappeared, thus making accurate evaluation impossible. *Forty-seven patients may be evaluated accurately.*

Leukorrhea: The amount of discharge was slight in 40, moderate in 7, copious in none. The color was white or gray white in 42, yellow in 3, green in one, and clear in one. Frothiness was noted in 10. The consistency was smooth. The odor was uniformly disagreeable. The pH was 5.2 on an average. These findings agree closely with those of Gardner and Dukes.

The discharge promptly ceased in 40 of the 47 patients when *H. vaginalis* vanished from the vaginal flora as a result of suitable therapy. In 2 patients the onset of leukorrhea coincided with the appearance of *H. vaginalis* in the vagina and vanished when the bacterium was eradicated. The discharge disappeared but the *H. vaginalis* persisted in 3 instances. In 2 the discharge persisted after *H. vaginalis* could no longer be recovered.

Ray and Maughan call attention to the fact that 19 of 68 patients with *H. vaginalis* vaginitis were completely asymptomatic. From the work of Gardner and Dukes it appears also that the bacterium may be present in the vagina without producing subjective leukorrhea.

Vaginitis: Redness, clinical evidence of vaginitis, was present in 34 of the 47 patients and absent in 13. It was diffuse and slight in most instances and punctate in a few. Prompt return to normal occurred when *H. vaginalis* was removed.

Gardner and Dukes and Ray and Maughan reported that redness of the vagina infrequently accompanied *H. vaginalis* vaginitis.

Since Leopold and Amies and Jones noted in their reports that the material for study was obtained from the cervices, it might be assumed that this bacterium was harbored there rather than in the vagina as observed by Gardner and Dukes. Our material was collected from the upper vagina in keeping with the latter's procedure so no direct cervical smears or cultures are available for reporting. However, some information can be offered which suggests that vaginitis rather than cervicitis is the basic lesion. Sixteen (34 per cent) of the 47 patients had strictly vaginal involvement since the cervix had been removed previously by complete hysterectomy. Of the other 31, redness of the vagina indicated vaginitis in 20 cases, but, of course, does not exclude the possibility of a coexisting cervical infection although none was evident.

Pruritus: Slight pruritus was complained of by 21 patients (44.7 per cent) while in 26 this symptom was lacking. One patient had severe vulvitis with redness, edema, and marked pruritus. In this patient, *H. vaginalis* was isolated from secretions scraped from the vulva but was not recovered from the vagina.

Gardner and Dukes reported mild itching or burning of the vulva in 31 per cent of the patients. Later they stated it occurred only occasionally. Deming also records pruritus as an infrequent symptom. Ray and Maughan list pruritus as mild in 26 (38 per cent) of 68 patients with redness or edema in only 5 patients.

We observed clinical evidence of vulvitis and vaginitis more frequently than was indicated by other authors.

The pruritus was relieved in 19 of the 21 patients when *H. vaginalis* was treated successfully.

Bacterial flora with H. vaginalis: Since any known pathogenic or potentially pathogenic bacterium could conceivably play a role in the production of leukorrhea, the flora in 45 of the 47 patients was studied. In the initial cultures made prior to treatment the relative incidence of the organisms was

as follows: diphtheroids, 71.1 per cent, nonhemolytic staphylococci, 42.2 per cent, lactobacilli, 24.4 per cent, hemolytic streptococci, 24.4 per cent, hemolytic staphylococci, 2.2 per cent (1 patient) and *E. coli*, 2.2 per cent (1 patient). In individual patients, following therapy, the flora was extremely variable. The incidence of the organisms following the eradication of *H. vaginalis* was approximately the same as the incidence on initial cultures, however. Diphtheroids, nonhemolytic streptococci, nonhemolytic staphylococci, lactobacilli, hemolytic staphylococci, and *E. coli* were present in approximately equal frequency both with and without *H. vaginalis* and were completely unrelated to the presence or absence of leukorrhea. Of the 11 patients (24.4 per cent) with hemolytic streptococcus initially, in 5 this organism disappeared simultaneously with *H. vaginalis* when treatment was instituted and it never reappeared. The specific role of the streptococcus or the *H. vaginalis* cannot be determined in these patients. In the remaining 6 patients the casual appearance and disappearance of this organism in the flora without respect to the symptoms indicate that the leukorrhea was not due to the hemolytic streptococcus. That this organism is not an important factor is borne out further by the fact that in 34 (75.6 per cent) of the patients, hemolytic streptococci were not present. When *E. coli* and hemolytic staphylococci were present, their numbers were insignificant in comparison to the numbers of the various other bacteria in the flora. And they, too, seemed to be unimportant because of this and also because they occurred so infrequently.

Treatment: Various medications were used locally in treatment of the *H. vaginalis* vaginitis and often several were used in a single patient. Terramycin with polymyxin B vaginal suppositories, one daily for 14 days, gave by far the best results. Used on 40 occasions, it resulted in the prompt eradication of *H. vaginalis* in 36 as determined by wet mount, Gram stain, and culture. A yeast-like fungus promptly appeared in the vaginal flora on 14 occasions following this therapy. Only in 5 did it produce symptoms, mild in 4 and severe in one. In 9 there were no symptoms or evidence of disease and no treatment was required. Because of the occurrence of *Candida albicans* subsequent to Terramycin-Polymyxin B therapy, we have, since completion of the study of this series of patients, utilized hexetidine* with excellent results.

In 3 instances, *H. vaginalis* disappeared from the flora without treatment.

Comment

Gardner and Dukes were successful on numerous occasions in isolating *H. vaginalis* in pure culture from primary specimen material upon Casman's blood agar medium as well as in thioglycolate broth. Cultivation of *H. vaginalis* in our laboratory, though with the use of the identical medium of the former authors, rarely resulted in such a pure culture phenomenon. Single colony isolates permitted us pure culture isolation, but stock culture maintenance for any one strain never exceeded two to three transfers.

Amies and Jones,[7] using a serum-yeast medium, experience no difficulty in maintaining stock cultures of *H. vaginalis* upon this medium. These authors were of the opinion that differentiation of colonial forms of *H. vaginalis* and fecal streptococci could not be distinguished purely upon morphological grounds. It seems to us, however, that the "eye" of a trained observer soon becomes familiar with the characteristics of the *H. vaginalis* colonial forms, at least upon the Casman medium, and can differentiate such colonies in a high percentage of instances.

We are in agreement with Amies and Jones as to the morphologic appearance of primary culture isolated strains in stained smears, viz.: thin straight or

*Sterisil vaginal gel, Warner-Chilcott Laboratories.

slightly curved rods, about 0.3 by 1-2 μ, invariably gram negative; upon transplants becoming highly pleomorphic. We have also observed, however, that many transplanted strains became gram variable, some to the point of being only gram positive and looking very much like small diphtheroids. This latter phenomenon caused us to question whether we had lost the *H. vaginalis* organism and picked up a diphtheroid organism instead. It is also worth noting that our original criteria for the diagnosis of *H. vaginalis* were rigidly adhered to throughout. As a result, Vibrio and filamentous gram-negative forms observed on direct specimen smears were placed in a separate category and not considered as *H. vaginalis.* Amies and Jones in their description of L forms of *H. vaginalis* have considered such morphological forms as part of the *H. vaginalis* pattern under certain circumstances and are probably correct in doing so. The scope of our purpose in this study did not permit us to carry this observation further.

Gardner and Dukes[11] have commented upon the presence of small diphtheroid organisms confusing the picture of *H. vaginalis* from initial specimen material and smear.

They[1] recovered *H. vaginalis* in 141 (12 per cent) of 1,181 routine office patients and later, Gardner, Dampeer, and Dukes[12] noted a similar ratio in 2,251 private office patients while the incidence was 33.9 per cent in Negro clinic patients. Wurch and Lutz, in a study of 500 women with leukorrhea, reported that 22 per cent had in the vaginal flora an organism which appeared to be the same as that described by Gardner and Dukes. In 39 per cent of 231 patients with acute vaginitis, Ray and Maughan isolated *H. vaginalis* and stated it was the predominant organism. Amies and Jones found *H. vaginalis* in 41 per cent of 829 smears submitted for study and in 5.1 per cent of 371 specimens cultured, but no clinical data were available to them. In our study 89 (42.2 per cent) of 211 patients with leukorrhea had *H. vaginalis* in the flora.

The variation in rates is consistent with the fact that all authors have not used identical methods in making surveys of patients. In patients with leukorrhea the variation may be accounted for by differences in samples studied and quite possibly by differences in interpretation of what constitutes leukorrhea by the patient or the physician, a point of great variability with which all of you are familiar. Regardless of this, it is apparent that *H. vaginalis* is frequently found in the flora of patients with leukorrhea and vaginitis.

Gardner and Dukes, in attempting to evaluate the pathogenicity of *H. vaginalis* in the human, set about to fulfill the postulates of Koch with the following results:

1. The vaginitis in 92 per cent of 138 patients with bacterial vaginitis was the result of infection with *H. vaginalis.*

2. *H. vaginalis* was isolated and grown in pure culture in all of the 141 patients comprising the group studied. In 85 of the 141 patients it was the only bacterium present on one or more occasions and in the remaining 56 it was the predominant organism.

3. Inoculations made directly from patients with *H. vaginalis* vaginitis to 15 uninfected volunteers resulted in 11 of the 15 developing clinical manifestations of the disease.

The inoculations from pure cultures of *H. vaginalis* to 13 normal women resulted in one woman developing the disease while the remaining 12 did not.

4. *H. vaginalis* was recovered by culture methods from the 11 volunteers in whom inoculations were made directly from infected women. A pure culture of *H. vaginalis* was obtained from the one woman inoculated with organisms obtained from pure culture of *H. vaginalis.* In 2 of the other 12 patients who did

not develop the disease, *H. vaginalis* was recovered in the cultures. (The authors believed that the inoculation of culture material was less efficient than the direct transfer because culture media can support the growth of *H. vaginalis* for only a few days.) Three husbands developed positive cultures after *H. vaginalis* vaginitis had been experimentally produced in their wives.

Efforts to determine the pathogenicity of this organism in experimental animals have been made. Lutz, Grooten, and Wurch[5] injected the bacterium intraperitoneally in mice and intradermally in rabbits. The mice showed no evidence of distress and survived. In the rabbits, there was no necrosis or evidence of infection. Amies and Jones inoculated rabbits, guinea pigs, white mice, and golden hamsters, using subcutaneous, intradermal, intravenous, intraperitoneal, and intracerebral routes. The rabbit was the only animal found to be susceptible to infection. Intradermal injection resulted in the formation of a circumscribed, raised, red lesion whose resolution required 10 to 15 days. They report that in some rabbits repeated intravenous injections produced fever, loss of weight, and dyspnea.

Clinical evidence of pathogenicity is suggested by the frequency with which this organism is the predominant one (or as reported by some, the only bacterium) in the vaginal flora of patients with bacterial vaginitis, and by the fact that the reports including ours note that the leukorrhea and vaginitis disappear when *H. vaginalis* disappears from the flora. In our investigation this took place in 42 of the 47 patients studied.

It is difficult to prove that a single organism is the cause of vaginitis and leukorrhea since the vaginal flora usually contains many types of bacteria, some possible pathogens, others not. In our study the flora varied considerably in individual patients over the year and one-half that cultures were made. No one organism was consistently found in association with *H. vaginalis* which might be considered capable of producing infection and leukorrhea. These bacteria appeared and disappeared from the flora without any rhyme or reason as far as leukorrhea was concerned. As a cause of leukorrhea in the patients studied, the bacteria, other than *H. vaginalis,* were obviously unrelated to the vaginitis.

Although we have excluded from considerations the cases in which trichomonads or *Candida albicans* coexisted with *H. vaginalis,* attention should be drawn to the fact such an association is not infrequent and has been noted by Gardner and Dukes (8.5 per cent of 141 patients with *H. vaginalis* had trichomonads, and 5 per cent of the 141 patients had Monilia), and Ray and Maughan (26.6 per cent of 91 patients with *H. vaginalis* had trichomonads, and 14 per cent of the 91 patients had *Candida albicans*). In our series these figures were 23.6 per cent and 6.7 per cent, respectively. In addition, 3 (3.4 per cent) of the 89 patients had *H. vaginalis,* trichomonads, and *Candida albicans* in the flora simultaneously.

It has been suggested that *H. vaginalis* is pathogenic in the male. Leopold obtained positive cultures of an organism similar or identical to the one being considered here from the urethras of 53 men, all of whom had mild-to-moderate prostatitis with or without urethritis. Of 9 men whose wives had positive *H. vaginalis* cervical cultures, the urine cultures revealed this bacterium in 4. Gardner and Dukes reported that *H. vaginalis* was obtained by culture from the urethras of 45 of 47 husbands whose wives had *H. vaginalis* vaginitis. Later, in a personal communication, Gardner[11] stated that 100 husbands of infected wives were submitted to urethral cultures and that almost all of them yielded *H. vaginalis* as the predominant organism. He doubts it is responsible for urethritis or prostatitis. Ray and Maughan recovered *H. vaginalis* from the

urethras of some of the husbands of infected wives. Amies and Jones, in examining stained smears, identified this organism in 8 per cent of 171 males with nongonococcal urethritis. It is not at all certain that *H. vaginitis* is capable of producing disease in the male generative tract, but it seems certain that this organism does inhabit the male urethra from whence it may be a source of infection in the female.

Conclusions

1. Following the procedures of Gardner and Dukes we have isolated from the vagina a small gram-negative, nonmotile bacillus apparently identical with the one described by them and designated *Hemophilus vaginalis.* The name, *Hemophilus vaginalis,* is accepted even though some aspects leading to its classification are still incomplete. We have not obtained pure cultures of this bacterium. Gardner and Dukes, on the other hand, have frequently obtained pure cultures.

2. This organism must be considered a cause of leukorrhea and vaginitis although its pathogenicity is not yet completely demonstrated.

References

1. Gardner, H. L., and Dukes, C. D.: Am. J. Obst. & Gynec. **69**: 962, 1955.
2. Leopold, S.: U. S. Armed Forces Med. J. **4**: 263, 1953.
3. Wurch, T., and Lutz, A.: Rev. franç. gynéc. et obst. **50**: 289, 1955.
4. Deming, J. E.: Northwest Med. **54**: 992, 1955.
5. Lutz, A., Grooten, O., and Wurch, T.: Rev. Immunol. **20**: 132, 1956.
6. Ray, J. L., and Maughan, G. M.: West. J. Surg. **64**: 581, 1956.
7. Amies, C. R., and Jones, S. A.: In press.
8. Thompson, L.: J. Bact. **31**: 82, 1936.
9. Henriksen, S. D.: Acta path. et microbiol. scandinav. **24**: 184, 1947.
10. Casman, E. P.: Am. J. Clin. Path. **17**: 281, 1947.
11. Gardner, H. L.: Personal communication.
12. Gardner, H. L., Dampeer, T. K., and Dukes, C. D.: In press.

Discussion

DR. H. CLOSE HESSELTINE, Chicago, Ill.—The organism under discussion, according to most classifications, is a genus or subgenus of a family of Bacteriaceae. Although the methods may vary somewhat in the classification, the genus (the Hemophilus) is a hemoglobinophil. These organisms became so labeled because hemoglobin has been looked upon as a requirement in the media. In the strict sense, certain organic iron compounds may be used in place of blood. The difficulty which Dr. Brewer and his colleagues encountered in obtaining a pure culture is one that confronts microbiologists not infrequently. Inhibiting or neutralizing factors on or dissolved out of the equipment, especially a soft glass, may account for pure culture failure. Substances in the source of the medium or preparation of it may be lethal to the organism. Difficulties in this type of study may arise when even minute but presumed unimportant chemicals, antigens, or antibodies are present on the equipment. To illustrate this point, *Hemophilus influenzae,* a related species, is usually grown better on media made from blood of rabbits or horses. The blood from sheep, goats, and cattle is less satisfactory and that from humans should not be used. It is claimed that heating blood for chocolate agar media destroys or removes inhibitory factors, but this may be questioned. There is also the need of maintenance of a favorable enzyme system.

The descriptions of the methods of study speak for themselves. A technical problem of isolation can be frustrating for organisms that are easily affected by unfavorable changes in the oxygen concentration. Very possibly thermal differences between incubator and room, or factors of light, or effects of unrecognized sound waves may be hurdles to cross. These points may be emphasized by the fact that certain strict anaerobes, such as *Bacillus melaninogenicus,* can be carried in pure culture, provided that transfers

to new plates be effected very rapidly and that restoration to strict anaerobiosis be immediate and other hostile conditions be controlled. On this basis the transplantation and re-establishment in proper nutritive environment, maintenance of the essential enzyme system, temperature control, and other states are critical factors. There can be little doubt that carrier states do exist in some individuals as the authors have shown.

One may ask further questions on the comparative values of in vitro and in vivo responses. All too often the in vitro studies cause misconceptions of specificity. It is anticipated that Dr. Brewer and his colleagues will continue their study of this clinical entity with the ultimate goal of better understanding of the entity per se, as well as the easy but exact diagnostic and specific therapeutic managements.

DR. E. STEWART TAYLOR, Denver, Colo.—I wish to ask about treatment of this infection. We have also been interested in this specific diagnosis and have found that the use of various antibiotic drugs, and especially the wide-spectrum drugs, sometimes initiates symptoms of vulvovaginitis that are more distressing than the original vaginitis. We have found that we can control Hemophilus vaginitis best with intravaginal sulfonamide cream. I wonder what recommendations you can add about the choice of treatment.

DR. BREWER (Closing).—We have found that the sulfonamide preparations were not as good, either in the sensitivity reactions or in the actual local application in the vagina. Terramycin with polymyxin B and some of the others were better. In the male, oral preparations have been used and are quite effective. One of the difficulties in diagnosis is that on occasion diphtheroids will cause confusion.

INFLAMMATIONS OF THE NONLACTATING BREAST*

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THE title is intended to include infectious mastitis, traumatic mastitis, and a variety of conditions in which an inflammatory process is considered in the differential diagnosis. Infections of the lactating breast are relatively common and their diagnosis and management are familiar to obstetricians and gynecologists. In the nonlactating breast the manifestations of inflammation are varied and the responsibility for the management of them is divided among several specialties. Since the breasts are a part of the reproductive system, it seems important that the gynecologist should be familiar with the lesions that may occur. No text brings this group of lesions together; therefore, it seems desirable to present them here for consideration.

Infectious Mastitis

Acute infections in the nonlactating breast are much more common than is generally recognized. When an infection develops in a location away from the areola, it usually behaves as a nonspecific infection in any other part of the body would behave. If, however, the infection involves the areola, recurrence is common and the infection may persist for weeks, months, or years. The tendency to become chronic because of location in the areola has received scant recognition in the literature. Kilgore and Fleming,[1] in 1952, emphasized that when an abscess occurs, so that either spontaneous or surgical drainage must be through the areola, or at its edge, it has a remarkable tendency to recur repeatedly, and to be highly resistant to a permanent cure, whatever the method of treatment.

The infectious process in the area of the areola may originate in the glands of the skin, or subcutaneous tissue, or in a duct of the mammary gland. It may be difficult to determine the point of origin of the infectious process but it may be assumed that the duct is involved primarily or secondarily in the abscesses and fistulas which are resistant to treatment. Involvement of a duct may not be the sole cause of the persistence of subareolar infections but it is an important feature.

Treatment of subareolar infections consists of adequate surgical care, identification of the infecting organism, demonstration of sensitivity to the different antibiotics, and use of the antibiotic indicated by the sensitivity test. The surgical procedure indicated varies individually from mere observation, aspiration, incision, and drainage to simple mastectomy. Kilgore and Fleming[1] reported 64 cases which had been followed from 2 to 20 years. They reported that in three-fourths of the cases there were from one to two to literally dozens

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of recurrences of abscess formation. They stress the importance of the infected duct and the necessity for removal of the duct. Simple mastectomy was performed in 9 of their 64 patients. Most of their patients were treated before antibiotics were available.

The most common organism found in the subareolar infections is a staphylococcus. Aerobic streptococcus is next in order of frequency. Anaerobic streptococci are less frequent invaders, but when they are present a special problem is created. The response to infection with the anaerobic streptococcus in the subareolar space resembles pelvic infection with the same organism. The systemic reaction is mild with little or no elevation of temperature and slight leukocytosis. Locally, tenderness is moderate. Brawny induration is characteristic. Fluctuation is not easily demonstrated. Microscopic examination of the abscess wall shows a lining granulation tissue on a fibrotic base. Inflammatory reaction can be demonstrated in the adjacent ducts and glands. The organisms are not highly virulent but the infections are resistant to treatment. The resistance is at least partly due to inaccessibility of the organisms. The heavy scar tissue prevents contact with the antibiotics on account of the poor blood supply. The thick wall of fibrotic tissue does not permit free drainage through an incision. In addition to incision and administration of antibiotics, it is desirable to keep the cavity open to permit granulation to proceed from the bottom until the cavity is closed. During this process irrigation with hydrogen peroxide is useful to counteract the anaerobic conditions. The clinical manifestations of infection with the anaerobic streptococcus are usually characteristic. Confirmation of the diagnosis by bacteriologic studies is helpful but they cannot always be obtained.

Tuberculosis

Tuberculosis of the breast is relatively uncommon when compared with the frequency of tuberculosis in other organs. It is invariably unilateral. It occurs in youth or middle age. Although some authors consider tuberculosis in other structures significant in the diagnosis of the infection in the breast, in my experience that association is unusual. While it may appear in a lactating breast, that association is also unusual. I have seen only one instance in which this occurred.

The first sign of the disease is usually a painless swelling. The lump enlarges slowly and at this stage the clinical resemblance to malignancy may be close. As the mass increases in size it becomes attached to the skin. Redness and tenderness of the area suggest infection. Liquefaction of the center of the mass accounts for a sense of fluctuation. At this point it may break through the skin, may be aspirated, or it may be incised. A history of repeated incision with recurring abscesses and sinuses strongly suggests the diagnosis of tuberculosis. Confirmation may be obtained by bacteriologic examination and animal inoculation.

The use of antibiotics has reduced the extent of surgical procedures in the treatment of tuberculosis as well as other infections of the breast. Failure to respond to the antibiotics is an indication that the lesion may not be an infection. Other inflammations may simulate infection of the breast.

Chemical Mastitis

Two uncommon conditions may be classified as chemical mastitis, namely, fat necrosis and plasma-cell mastitis. Their etiology is obscure but the theory that they are a response to fatty material is acceptable. Since both lesions

either show evidence of inflammation or resemble an inflammatory process at some phase of their development, they are included in the differential diagnosis of inflammation.

Fat Necrosis.—Fat necrosis occurs in large, fatty, or pendulous breasts. In the early phase it may be mistaken for inflammation and in their later phase for carcinoma. Discovery of a lump brings the patient for examination. She may recall a definite trauma or she may have a vague recollection of trauma or none at all. When the lump is tender and painful a question of inflammation may arise. Absence of redness, local elevation of temperature, and constitutional symptoms exclude a diagnosis of inflammation. In the later phase, exclusion of a diagnosis of carcinoma offers more difficulty. Histologically, there is destruction of fat with phagocytosis and foreign-body giant cells. In some instances the number of plasma cells present has suggested a diagnosis of plasma-cell tumor. Fat necrosis may be found with resolving hematomas or abscesses. The accepted treatment for fat necrosis is local excision. The early phase when the symptoms and signs suggest the possibility of inflammation is relatively short.

Plasma-Cell Mastitis.—This is an inflammatory lesion of the breast which occurs during the reproductive period. Nonlactating parous women are the usual subjects of this condition. Since less than 100 cases have been reported it may be considered rare. It has been recognized as an entity only twenty-five years, however. Many observers do not consider this lesion as an entity and, therefore, do not report their observations.

The clinical picture presented depends upon the phase in which the condition is first observed. The earliest manifestation is inflammation. It often begins suddenly with pain, tenderness, diffuse swelling of the breast, and mild constitutional symptoms. The intensity of the symptoms varies considerably, but mildness of symptoms is usually characteristic. The patient may recall the signs of inflammation only vaguely when she is observed for the first time in the later stage of the disease. The extent of the involvement of the breast usually includes more than one quadrant and may involve the whole breast. The acute phase subsides and a residual mass in the deeper tissue remains. Retraction of the nipple, fixation to the skin and surrounding tissue are common. In this phase the differential diagnosis from cancer becomes important. The duration of the process varies from weeks to months and even years. Sometimes the mass spontaneously disappears. Frequent enlargement of the axillary glands is not significant.

The etiology of plasma-cell mastitis remains obscure. Bacterial studies have not disclosed any specific organism and cultures are usually negative for any bacteria. Chemical irritation has been considered favorably as a cause of the lesion. Extravasation of fatty material through the wall of the ducts induces the inflammatory reaction. Sometimes definite trauma is noted. Minor traumas are so common in a woman's life that they are not considered important enough to report. Perhaps one might assume a slight trauma to cause a break in the wall of the duct and allow the fatty material to seep through the wall. If trauma is the cause of the extravasation of the fatty material, plasma-cell mastitis might be included among the traumatic lesions.

The histologic characteristics of plasma-cell mastitis are quantities of plasma cells, giant cells, proliferation and piling up of duct epithelium. Since plasma cells are present in a variety of conditions in which chronic inflammation is a feature, objection to the acceptance of plasma-cell mastitis is an entity seems justified, in fact, plasma cells are not pathognomonic of anything. It is not a surprise, therefore, that plasma-cell mastitis has been confused with such other conditions as tuberculosis, suppurative mastitis, fat necrosis, and

carcinoma. The chronicity of the condition justifies conservatism in the treatment of the inflammatory phase with careful observation to rule out a more serious condition.

Traumatic Mastitis

Traumatic mastitis is a mild inflammation of breast tissue in response to repeated slight trauma. It occurs most frequently during the reproductive years, but it may appear occasionally after the menopause. It is most common in the third and fourth decades when the physiologic activity of the breast is high. The onset is the discovery of a tender area or a lump in the breast. The patient may have found the lump herself because her attention was attracted to the tender area, or she may have accidentally felt the lump. Publicity for cancer detection induces an increasing number of women to examine their breasts routinely so that many patients seek advice because of any lump on the skin or in the breast that they may have found. The woman may have had a trauma to her breast and examined it to find the result of the trauma.

The only systemic manifestation of traumatic mastitis is the emotional response. The temperature is not elevated. The blood is not changed. Local examination reveals one or more lumps in one or both breasts. The skin over the area is not changed except for occasional redness or pressure marks from the clothing. Tenderness over the mass varies, but it is usually slight. The margins of the mass are not sharply defined. Induration is not extreme but it is sufficient to show a distinct difference between the mass and the normal breast tissue. The size ranges from a few millimeters to several centimeters with an average of about 2 cm. The shape varies but it is usually spherical. When it occurs in the lower part of the breast it is often elongated transversely.

Microscopic examination is seldom obtained because the condition does not justify removal. When a specimen is examined the most striking change is edema. There may be a slight increase in vascularity and slight infiltration by leukocytes.

When traumatic mastitis is suspected, the diagnosis may be confirmed by bandaging the whole breast to prevent any manipulation. After several days the bandage is removed and if the mass has decreased any neoplasm may be excluded. If the inciting trauma is located and removed, the mass subsides.

That traumatic mastitis may occur came to my attention for the first time in 1913. A young woman, a hairdresser, came to the University of California Out-Patient Department complaining of tender lumps in the breast. Two discrete lumps in the right breast were located in the deeper tissues but were not attached to the skin. My diagnosis was multiple fibroadenomas. She was given an admission request to arrange to have the tumors excised. A month later she returned for observation and to tell me that my diagnosis was incorrect. The lumps were no longer palpable though she had not had them removed. She attributed the lumps to too much handling by her friends. When she avoided all manipulation the lumps disappeared. Soon after this experience another patient, a seamstress, complained of a tender lump in the left breast. In her occupation she was constantly bending over a corset stay. The stay was removed and in a short time the lump disappeared.

Reflection on the two observations just mentioned indicated a definite relation between repeated trauma and the temporary lumps in the breasts. It seemed logical to call the condition traumatic mastitis. A search of the literature at that time disclosed that Cheatle,[2] in 1911, has described a similar condition which he called chronic traumatic mastitis. He wrote, "The term mastitis is used in spite of the fact that no blood changes are found; no change

in temperature; no enlargement of the lymphatic glands." He also noted recovery in all cases so there was no justification for removing a specimen. He noted the relation of the lumps to the irritation of corset stays. Since that time I have accepted traumatic mastitis as an entity because it fits the condition better than any other term I know.

Protection of the breast by a bandage which is large enough to prevent all trauma establishes the diagnosis. Tenderness, the symptom and sign most suggestive of inflammation, disappears. Suspicion of cancer is no longer justified when the lump disappears. To maintain relief it is necessary to discover the source of trauma. When the relation of trauma to the lump is explained to the patient she can frequently identify the probable cause. Enumeration of some of the common causes may help to solve the individual problem. One may mention the possibility of occupational trauma such as carrying books or other hard objects against the breast. Just as corset stays were formerly a source of irritation, one of the most frequent causes of trauma today is a brassiere. Inspection of the brassiere worn at the time of examination should be supplemented by information concerning brassieres worn at other times. Search for point or line pressure is the important feature of the examination of the brassiere. The irritating trauma varies with the individual. With the cooperation of the patient the source of the irritation can usually be discovered.

Inflammatory Carcinoma of the Breast

Inflammatory carcinoma of the breast is a term applied to a cancer associated with manifestations of inflammation. The tumor is not a specific type, but it grows rapidly and is very invasive. The inflammatory manifestations include induration, redness, increased local heat, pigskin or orange-peel appearance, tenderness, and sometimes local pain. Most of the inflammatory signs may be explained by invasion of the subdermal lymphatics and capillary congestion, but bacterial infection is rarely a factor. Rapid extension may soon involve the entire breast and spread to the neck and arm, resembling erysipelas, hence the reference to the condition as erysipeloid carcinoma. Systemic symptoms are lacking.

In the experience of some authors the disease is more common during pregnancy or lactation. The few that I have seen were in nonlactating breasts. In a report from the Hospital of the University of Pennsylvania by Rogers and Fitts,[3] among 45 women 50 per cent were postmenopausal. In their review of a 26 year period there were 1,774 patients treated for pathologically proved carcinoma of the breast. Of these, 46, or 2.6 per cent, had primary inflammatory carcinoma of the breast. One of their patients was a male. The age range was from 26 to 80, with an arithmetic mean age of 49.9 years.

The prognosis of the disease is always grave on account of the malignancy. The inflammation is secondary and not serious. Unfortunately, valuable time has been wasted too often while the inflammation was treated and the cancer overlooked. Agreement concerning the best method of treatment of inflammatory cancer of the breast has not been reached. Many authors consider the condition to be inoperable for they believe that all such lesions are fatal regardless of the treatment and that operation may disseminate the cancer and hasten the end. Rogers and Fitts report one patient alive and well 8 years after a radical mastectomy and they found other reports of 5 year survival after radical mastectomy.

Chronic Cystic Mastitis

Chronic cystic mastitis may be mentioned in passing because the word mastitis denotes inflammation. In reality inflammation is not a characteristic

of any of the various lesions included under the general term chronic cystic mastitis. Since the presenting symptom of these lesions may be pain, tenderness, or swelling it sometimes becomes necessary to rule out inflammation. The absence of the other cardinal symptoms, local heat and redness, excludes the diagnosis of inflammation. The main problem for differential diagnosis is the possibility of the presence of cancer which is not pertinent to this discussion.

The age at which chronic cystic mastitis occurs is consistent with either cancer or inflammatory lesions. Many of the lesions present no symptoms. A lump is discovered by the patient or by the physician in a routine examination. The pain and tenderness of inflammation tend to be constant as compared with the pain and tenderness of chronic cystic mastitis which is cyclic in relation to menstruation. Furthermore, one nodule may be tender and a similar nodule in the same breast not tender. In general the character of the pain and tenderness is so distinctive that one seldom experiences any difficulty in ruling out a diagnosis of inflammation.

Scleroderma

Dermatologic lesions may appear on the breast just as on any other part of the surface of the body. When the skin of the breast is involved at the same time as other areas, the diagnosis of the lesion of the breast does not present a particular problem. If, however, the breast bears a solitary lesion, the diagnosis may be difficult, as illustrated by a patient who had localized scleroderma.

A white woman, aged 56, complained of a lump in the right breast which she feared was a cancer. She had noticed slight tenderness and redness of the area involved. No systemic symptoms were mentioned. On examination the temperature was not elevated. The leukocytes were not increased. The findings on physical examination were not important except the lesion on the breast. On the inner lower quadrant of the right breast there was an oval area which measured 3 by 5 cm. The pale red edge of the area was sharply defined and slightly raised above the surrounding skin. The red margin shaded into the smooth white central portion of the lesion. The area was slightly tender on palpation which suggested the possibility of an inflammmatory process. The whole area was indurated. The condition was confined to the skin and subcutaneous tissue.

Discussion of the differential diagnosis brought several opinions. Cancer was suggested but ruled out because the glandular tissue of the breast was not involved, as the condition was limited to the skin and subcutaneous tissue. Chronic inflammation was considered because of the redness and tenderness, but these symptoms were minimal. The dermatologists maintained that we were dealing with localized or circumscribed scleroderma (morphea). This diagnosis was supported subsequently by the appearance of a similar plaque on the skin lateral to the breast. Both lesions were observed for 4 years. After the first few weeks the redness disappeared, the surface of the plaque was smooth, the induration persisted, and the tenderness subsided. After 4 years of quiescence a third lesion similar to the other two plaques appeared over the axillary portion of the same breast.

Localized scleroderma is a disease of unknown origin. It is benign, self-limited, and has no influence on the span of life. There is no specific treatment. Localized scleroderma is not common and on the breast it is rare. Christianson and others[4] reported 83 cases of morphea. They stated that while the condition occurs on the trunk it is not found on the breast.

Comment

A summary of the topics presented is not practical because of the diversity of the inflammations and processes resembling inflammation. The female breast is an important visual focal point of femininity. Anything that threatens to mar or sacrifice that evidence of femininity is a justifiable cause for anxiety. The significance of the anxiety is not always appreciated by the physician consulted, although it is very important to the patient. Since the conditions which have been presented rarely threaten life, the management of these conditions may include due consideration for preservation of natural structures. Thoughtfulness in diagnosis and conservatism in treatment will earn the gratitude of the patient.

References

1. Kilgore, A. R., and Fleming, R.: California Med. 77: 190, 1952.
2. Cheatle, G. L.: Brit. M. J. 1: 492, 1911.
3. Rogers, C. S., and Fitts, W. T., Jr.: Surgery 39: 367, 1956.
4. Christianson, H. B., Dorsey, C. S., O'Leary, P. A., and Kierland, R. R.: A. M. A. Arch. Dermat. & Syph. 74: 629, 1956.

Discussion

DR. JOHN B. MONTGOMERY, Philadelphia, Pa.—Not since 1925 has a paper on disease of the breast been included in our scientific program. Only three papers were presented during the previous 50 years. This undoubtedly is indicative of the attitude of the fellowship, a large majority of whom, like myself, probably regard the surgical treatment of breast lesions as the domain of the general surgeon. However, this same attitude certainly does not apply to our interest in the diagnosis of the common lesions in the breast where cancer is likely to occur more often than in the uterus. The very nature of our specialty makes it mandatory that we maintain a keen interest in breast problems and that we participate actively in the campaign for the early diagnosis of breast cancer.

Dr. Pratt has briefly reviewed the salient clinical features of inflammations of the nonlactating breast that result from infection, trauma both physical and chemical, carcinoma, hormone stimulation, and scleroderma. Some of the lesions discussed are not true inflammations but are included because they present clinical features that may lead to confusion in diagnosis. With the exception of chronic cystic mastitis and traumatic mastitis, the lesions discussed are not encountered frequently.

Although in Dr. Pratt's experience infections in the nonlactating breast are much more common than is generally recognized, there are few papers devoted to this subject in the literature. These deal almost entirely with recurrent infections beneath the areola. Caswell and Burnett recently have reported 6 cases associated with congenital inversion of the nipple. All the patients have remained well 8 to 30 months after interval excision of all diseased tissue with the overlying skin and adjacent base of the involved nipple. Many subareolar lesions probably result from distention and obstruction of one or more terminal ducts and a subsequent inflammatory reaction due to the cellular material and debris within the duct. This lesion, called comedomastitis by Dockerty and mastitis obliterans by Payne, has been further clarified by Haagensen under the term mammary duct ectasia. He has collected and studied 40 cases over a period of years. Thinning and eventual rupture of the distended duct with extravasation of lipid material into the tissues results in a peculiar inflammatory process, the end result of which he believes is plasma-cell mastitis.

Dr. Pratt has pointed out that these inflammatory lesions in the region of the areola have two common characteristics. They tend to recur and they frequently present clinical features suggestive of malignancy. In the acute suppurative stage, adequate drainage is

essential. Sometimes a wide transverse incision beneath the breast, as well as a deep incision into the abscess cavity with through-and-through drainage, may be required to accomplish this. During an interval phase complete excision of the residual fibrotic lesion, including the adjacent base of the nipple, should prevent a recurrence. When the lesion is clinically suggestive of malignancy, treatment with antibiotics and other conservative measures should never provide an excuse for undue delay in establishing a definitive diagnosis by biopsy.

Fat necrosis has been discussed under the heading of chemical mastitis on the assumption that the inflammatory reaction and the firm tumor that often results are due to local irritation as a result of the breakdown of fat. Whether traumatic mastitis is of similar origin has not been made clear. The early pathologic picture in fat necrosis is one of hemorrhage and induration which finally forms a firm tumor attached to the skin. When seen in the early stage with signs of inflammation, one may temporize for a few days but all authors agree with Dr. Pratt that the mass should be excised and examined histologically.

Inflammatory carcinoma has been included in this discussion because the unusual spread of this lesion presents a clinical picture of acute inflammation that may deter biopsy and delay definite diagnosis.

Chronic cystic mastitis has been discussed because the word "mastitis" denotes inflammation. Dr. Pratt clearly points out, however, that an inflammatory tissue reaction does not occur and that these lesions rarely present a serious problem in differential diagnosis from true inflammatory lesions. Many authors believe that this confusing term should be abandoned in favor of the more accurate term "cystic disease of the breast." Although the subject of Dr. Pratt's paper did not permit further discussion of the problem of cystic disease, it is interesting and important to note that many authors now agree that the incidence of cancer is higher in women with previous benign lesions in the breast.

Throughout his discussion Dr. Pratt has rightly emphasized accuracy of diagnosis and a thoughtful approach to the management of inflammatory breast lesions. He emphasizes conservatism and the preservation of the natural structures of the breast, the destruction of which is a cause for anxiety and unhappiness in many women. However, I am sure that Dr. Pratt will be the first to agree that conservative management of these lesions must not be permitted to interfere with early and adequate biopsy of any lesion where the diagnosis of carcinoma is a reasonable possibility.

DR. PRATT (Closing).—This paper was presented because I feel that, in general, lesions of the breast do not receive the attention that they should. Responsibility is divided among the specialists. The usual surgeon's approach is that, if he finds a lump, it must be removed. The general practitioner takes care of some of the lesions. *Many women are hesitant about having their breasts examined but they come repeatedly to the gynecologist for total check-up and it seems to me those visits should be used as an opportunity by the gynecologist to examine the breasts.* Although breasts are a part of the reproductive system, examination of them has been neglected. By careful attention to the diagnosis, particularly of traumatic mastitis, and by conservatism, the gynecologist can save unnecessary operations on many, many women.

THE EFFECT OF ESTRONE AND PROGESTERONE ON THE GROWTH OF EXPERIMENTAL ENDOMETRIOSIS IN RHESUS MONKEYS*†

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HUMAN external endometriosis, as a benign process, has many peculiarities. Its growth is limited to the years of menstrual function and this fact has implicated estrogens as an important factor, much as estrogens have been linked to the growth of benign fibromyomas of the uterus. Progesterone and its intermittent withdrawal have received little attention in any of the discussions of external endometriosis, despite the established facts that progesterone withdrawal from an estrogen-stimulated endometrium results in menstruation and that ectopic endometrium is histologically similar to the normally located endometrium. Since ectopic endometrium, under favorable circumstances, undergoes cyclic hormone changes, is it possible that progesterone withdrawal from this estrogen-stimulated endometrium results in "menstruation" into the tissues, implantation of viable endometrial fragments and growth? In order to test this hypothesis a group of rhesus monkeys (*Macaca mulatta*) were castrated and endometrium was surgically implanted to four areas in each animal. The animals were divided into four groups and periodically studied: Group I, no hormones; Group II, constant estrone; Group III, constant estrone and constant progesterone; Group IV, constant estrone and intermittent progesterone.

We, together with Te Linde,[6, 10] have reported studies with experimental endometriosis in rhesus monkeys which indicate that the menstrually discharged fragments of endometrium are viable. Also one of us (R. B. S.) with Te Linde[8] reported 4 clinical instances of human endometriosis which seemed most logically explained by viability of these shed and transplanted fragments of endometrium. In another study we[7] found that excessive amounts of diethylstilbestrol, over a period up to 2 years, did not cause disappearance of the experimentally produced endometriosis in uncastrated monkeys; in fact, 2 of the 4 animals showed hyerplasia in both the normally located and the ectopic endometrium and in 3 of the 4 animals uterine bleeding was accompanied by bleeding in the areas of endometriosis.

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Material and Methods

Adult, normally menstruating female rhesus (*Macaca mulatta*) monkeys were used. The animals were surgically castrated and fragments of endometrium (plus a small amount of underlying myometrium) were obtained by hysterotomy. Endometrial transplants were attached to the following four areas by means of black silk sutures: (1) the anterior surface of the uterus, (2) within the right broad ligament, (3) the serosal surface of the rectosigmoid bowel, and (4) the anterior abdominal wall beneath the rectus fascia.

The monkeys were then divided into four groups according to the following treatment plan:

Group I. No hormones

Group II. Aqueous suspension of estrone, 0.25 mg., intramuscularly twice weekly

Group III. Aqueous suspension of estrone, 0.25 mg., twice weekly. Progesterone in sesame oil, 6 mg. (0.25 c.c of 25 mg. per cubic centimeter), intramuscularly, 6 days out of every 7 days

Group IV. Aqueous suspension of estrone, 0.25 mg., intramuscularly, twice weekly. Progesterone in sesame oil, 6 mg. (0.25 c.c of 25 mg. per cubic centimeter), intramuscularly, daily for 5 days, the courses repeated beginning the twentieth day after evident or expected withdrawal bleeding

The animals were caught daily and tested for vaginal bleeding. Surgical exploration was performed one to three times and the gross lesions observed. One or more areas were partially excised for histologic study. An effort was made to do at least one of the exploratory procedures during an episode of vaginal bleeding. Five monkeys died within 4 to 21 months; the remaining 8 animals have been followed up to 37 months, but only 6 of these are now living.

Results

Group I. No Hormones.—

Monkey 941: Castration and endometrial transplantations were done on Feb. 22, 1954. There were two episodes of scant vaginal bleeding. The animal died of widespread tuberculosis 5 months later. Two tiny (2 to 4 mm.) transplants were identified, one in the uterine wall and one in the right broad ligament. Both of these showed rather inactive but healthy endometrial glands and stroma (Fig. 1).

Monkey 942: Castration and endometrial transplantations were done Feb. 22, 1954. There were no subsequent episodes of vaginal bleeding. Exploratory operation after 8 months showed no gross evidence of transplants. A second exploration was performed after 31 months and tiny white scars were found in the right rectus muscle, the anterior uterine wall, and the right broad ligament. A small focus of inactive, although not atrophic, endometrial glands and stroma was found in the right rectus scarred area.

Monkey 958: Castration and endometrial transplantations were done on Sept. 28, 1954. There were no episodes of vaginal bleeding. The animal was found dead of unexplained cause after 7 months. None of the endometrial transplants could be found grossly or microscopically.

Group II. Constant Estrone.—

Monkey 943: Castration and endometrial transplantations were done on Feb. 22, 1954. There were four episodes of vaginal bleeding (8, 11, 13, and 14 months after transplantations). An exploratory operation on the third day of vaginal bleeding, 8 months after the original transplantations, showed 6 to 8 mm. whitish nodules in all areas of transplantation. Biopsies of three of these areas demonstrated active, proliferative endometrial glands and

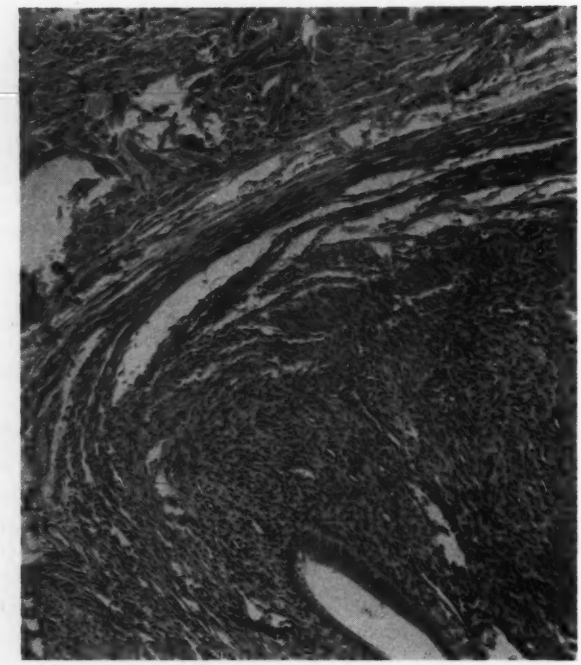


Fig. 1.—Monkey 941. Atrophic endometrial transplant in right broad ligament 5 months following surgical transplantation and castration. The animal did not receive hormones. (×100.)

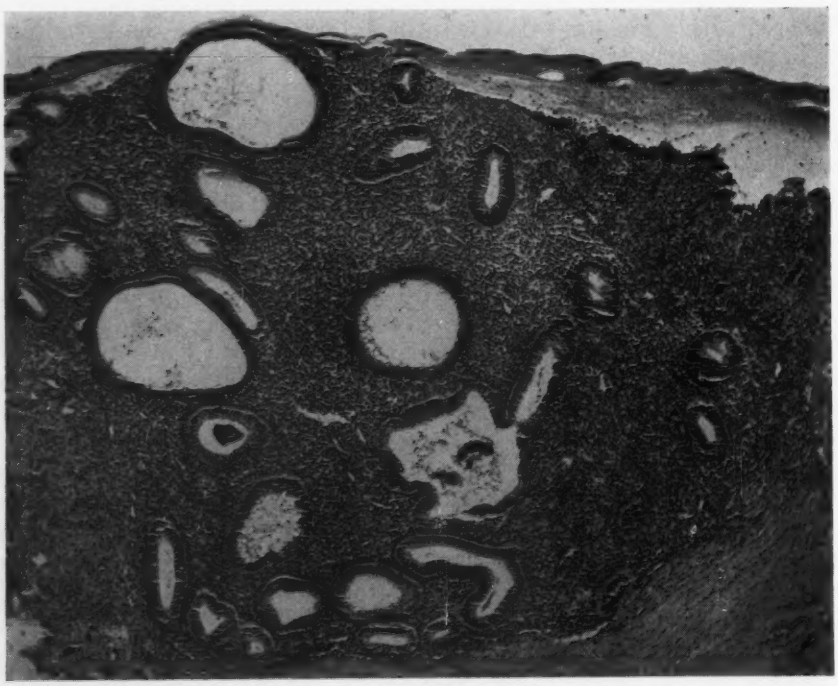


Fig. 2.—Monkey 943. Nodule of endometriosis in uterine wall showing a pattern of hyperplasia. Biopsy obtained 25 months following surgical transplantation and castration and twice weekly estrone injections. (×50.)

stroma. There was no gross or microscopic evidence of bleeding in the endometriosis. At an exploratory operation after 25 months the nodules were 6 to 10 mm. in size and the nodule on the uterus was chocolate colored. This nodule on the wall of the uterus microscopically showed a pattern of hyperplasia (Fig. 2).

Monkey 944: Castration and endometrial transplantations were done on Feb. 22, 1954. There were nine episodes of vaginal bleeding over the subsequent 31 months. After 15 months and on the second day of vaginal bleeding only two white, 1 mm. nodules were identified. There was no gross evidence of bleeding in the areas of endometriosis and the biopsy of the lesion in the sigmoid showed a proliferative type of endometrial tissue without the presence of old pigment. After 31 months three transplants were identified grossly; the largest was on the anterior surface of the uterus, about 5 mm. in diameter; however, a biopsy of this nodule was negative for endometrial tissue. After 37 months this animal died of extensive tuberculosis and active endometriosis was found in the uterine wall and the sigmoid musculature.



Fig. 3.—Monkey 960. Uterine wall endometriosis 18 months after surgical transplantation and castration. This animal received injections of estrone twice weekly and progesterone 6 days each week. (×50.)

Group III. Constant Estrone and Constant Progesterone.—

Monkey 945: Castration and endometrial transplantations were done on Feb. 22, 1954. There were 19 episodes of vaginal bleeding over the following 37 months. After 14 months, a laparotomy was performed on the first day of an episode of vaginal bleeding. All areas of endometrial transplants were seen, varying from 1 to 5 mm. in size. Biopsies of three areas showed no old blood pigment, a small area of fresh hemorrhage (traumatic?) in one specimen, and an endometrium with rather low epithelium and loose stroma but no definite secretory activity. After 31 months all lesions were again seen, varying from 1 to 4 mm. in size. Biopsies disclosed pigment-laden macrophages in the endometriosis of the rectus muscle. After 37 months this animal died of tuberculosis; all areas of transplantation were identified. The nodules were 6 to 8 mm. in size and microscopically showed regional extension. The bowel lesion extended as a 6 mm. polyp into the lumen, encased in fibromuscular tissue and covered by bowel mucosa.

Monkey 946: Castration and endometrial transplantation were done on Feb. 22, 1954. There was one episode of vaginal bleeding and the animal was found dead after 13 months. Autopsy did not disclose the cause of death. All four areas of transplanted endometrium were recognized as whitish nodules 3 to 4 mm. in diameter. Microscopically the glands and stroma were proliferative and the nodule of the anterior uterus showed considerable local pseudopodic spread.

Monkey 947: Castration and endometrial transplantations were done on Feb. 23, 1954. There were no episodes of vaginal bleeding and the animal died of widespread tuberculosis after 4 months. All the intra-abdominal transplants were small but contained active endometrial glands and stroma.

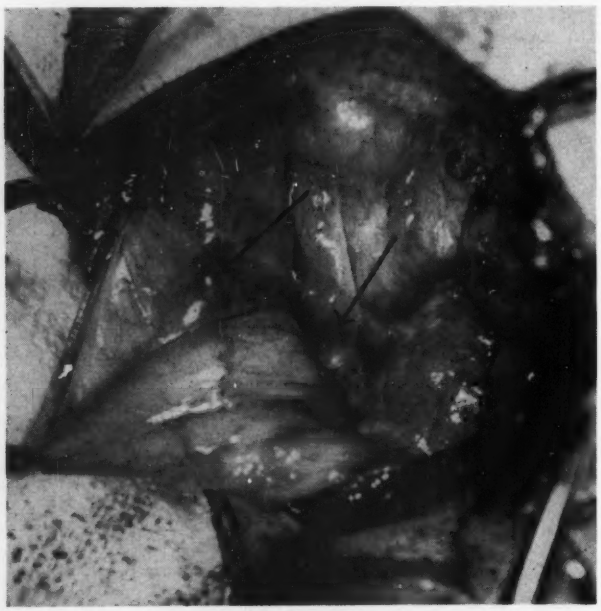


Fig. 4.—Monkey 948. Gross appearance of two endometrial transplants, as shown by the arrows. This was 13 months after the surgical transplantation and castration. The animal received injections of estrone twice weekly and progesterone cyclically. The abdominal exploration was done on the third day of vaginal bleeding.

Monkey 960: Castration and endometrial transplantations were done on Sept. 28, 1954. There were seven episodes of vaginal bleeding until an exploratory laparotomy 18 months later. Two transplants of 1 to 3 mm. were recognized which showed an active glandular epithelium and loose stroma (Fig. 3). The animal died of widespread tuberculosis 21 months after the original surgery and no gross or microscopic endometriosis could be found.

Monkey 963: Castration and endometrial transplantations were done on May 3, 1955. There were four episodes of scant vaginal bleeding until an exploratory operation 16 months later. Tiny 1 to 5 mm. nodules were found at the transplant sites and the rectus muscle transplant showed active endometriosis by biopsy study.

Group IV. Constant Estrone and Intermittent Progesterone.—

Monkey 948: Castration and endometrial transplantations were done on Feb. 23, 1954. There were eight episodes of vaginal bleeding until an exploratory laparotomy was done on the third day of bleeding, 13 months after the original operation. The transplants were 5 to 10 mm. in size and purplish or chocolate colored (Fig. 4). Microscopically there was

a lush growth of endometrial glands and stroma with some menstruation-like disintegration seen in the biopsy of the abdominal wall (Fig. 5). Evidence of old and fresh hemorrhage was present. After a total of 26 episodes of bleeding and 25 months after the original transplantations another laparotomy showed very similar gross and microscopic findings (Fig. 6).

Fig. 5.



Fig. 6.

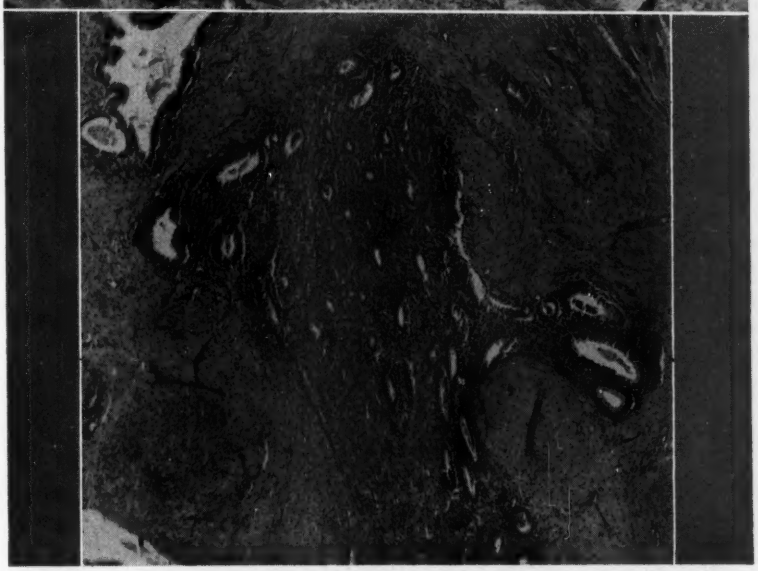


Fig. 5.—Monkey 948. Endometriosis of the abdominal wall as shown grossly in Fig. 4. Note the disintegration and hemorrhage at the lower border. Biopsied on the third day of an episode of uterine bleeding. (×50.)

Fig. 6.—Monkey 948. Endometriosis of the abdominal wall 25 months after original transplantation. Note active, pseudopodic growth. (×50.)

Monkey 949: Castration and endometrial transplantations were done on Feb. 23, 1954. Eight months later and after seven episodes of vaginal bleeding an exploratory laparotomy was done on the first day of bleeding. Three tiny nodules were identified and bowel was adherent over a 1 cm. puckered and pigmented area on the anterior uterine wall (Fig. 7). Biopsies from two areas showed a secretory endometrial pattern with one zone of menstruation-like disintegration. Exploratory operations were done again 20 months and 31

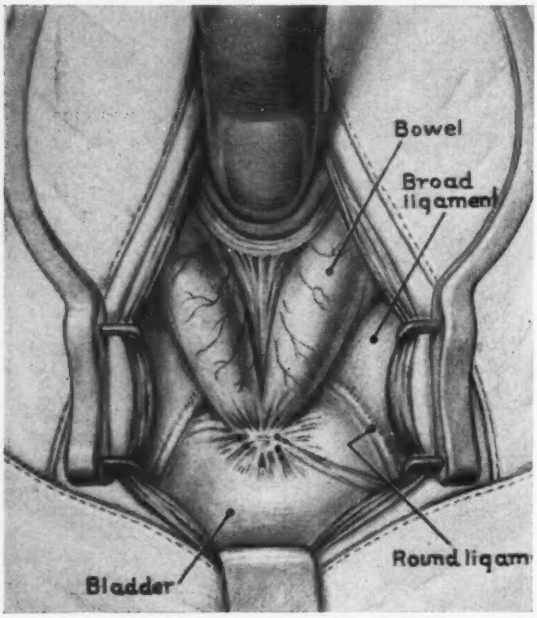


Fig. 7.—Monkey 949. Illustration of scarred area with old pigment on the uterine surface and adherent loop of bowel. This was 8 months after the original surgical transplantation and castration. The animal received injections of estrone twice weekly and cyclic progesterone.

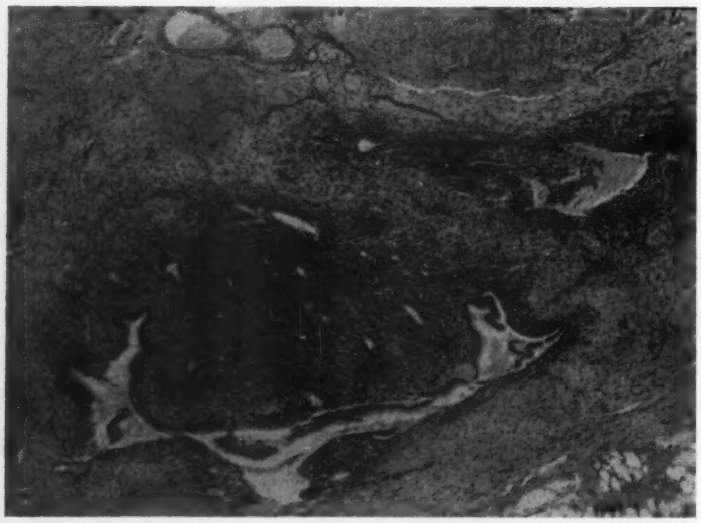


Fig. 8.—Monkey 949. Microscopic pattern of endometriosis in the broad ligament, 20 months after the original transplantation and castration. Estrone and intermittent progesterone were given. Many pigment-laden macrophages are present about this area of endometriosis, although they cannot be seen at this power. (×50.)

months after the original procedure (total of 34 episodes of vaginal bleeding). Grossly the nodules were 3 to 6 mm. in size and pigmented. There were numerous adhesions to the intra-abdominal transplants. Microscopically there was a lush growth of endometrial glands and stroma, old pigment, and adjacent fibrous tissue reaction. Fig. 8 shows the endometriosis of the right broad ligament after 20 months.

Monkey 950: Castration and endometrial transplantations were done on Feb. 23, 1954. Over the following 31 months there were 25 episodes of vaginal bleeding. Exploratory operations were performed 9, 21, and 31 months after the original surgery. Tiny scars were seen in the transplantation sites and tiny foci of endometrial glands were found by biopsy in two areas after 9 months; after 31 months there were intra-abdominal adhesions but no recognizable transplants except for a 6 mm. yellowish nodule in the abdominal wall. This nodule proved to be an abscess in an area of endometriosis. The animal was sacrificed after 37 months. All transplants were identified, either as small scars or nodules up to 6 mm. The anterior uterine nodule was chocolate colored; it was the fourth day of withdrawal bleeding. All nodules showed active endometriosis with local spread by infiltration; the anterior uterine nodule showed foci of secretory endometrium and areas of definite menstruation-like desquamation. The uterine mucosa was a menstruating type with beginning repair.

Summary of Results

Thirteen adult female rhesus monkeys were castrated and endometrium was surgically excised and transplanted to the anterior uterine serosa, the right broad ligament, the serosal surface of the rectosigmoid, and the anterior abdominal wall. The animals were divided into four groups for a study of the effect of administration of patterned and near-physiologic doses of hormones as follows: Group I, no hormones; Group II, constant estrone; Group III, constant estrone and constant progesterone; Group IV, constant estrone and intermittent progesterone.

The animals have been followed by periodic laparotomy and biopsy up to 37 months; 7 of the animals died in 4 to 37 months. The animals were checked daily for vaginal bleeding: Group I, 0 to 2 episodes; Group II, 4 to 9 episodes; Group III, 0 to 14 episodes; and Group IV, 25 to 34 episodes. The transplants were subsequently identified grossly and microscopically in at least one of the areas of all the animals except one of the three in Group I. Therefore, even without exogenous hormones, the transplants lived in 2 of the Group I animals. Endometrial hyperplasia developed in the endometriosis of one of the 2 monkeys in Group II. Old or recent hemorrhages were evident in at least one of the animals in Groups II, III, and IV. In 2 of the 3 monkeys in Group IV, the gross lesions were two to three times as large as those in Groups II and III; there was striking evidence of recent and old hemorrhages. One of the animals in Group IV had, for unknown reasons, a less marked growth with abscess formation in one transplant. Thus far, all growth and spread have been localized to the vicinity of transplantation with no suggestion of extensive local or distant spread. The injections will continue for at least two more years before the remaining animals are sacrificed and fully autopsied. The autopsy studies will include pelvic lymph nodes.

Comment

The clinical behavior and growth of external endometriosis have many apparent vagaries. From our clinical experiences we have observed the following:

1. It is a disease limited in its benign manifestations to the years of menstrual function.

2. It has not been identified before the menarche and it becomes atrophic and stagnates after the menopause.

3. The incidence increases as childbearing is delayed.

4. Several years (5?) without bearing of a child predispose to the symptomatic growth of the disease.

5. Pregnancy allays the symptoms of the disease and complications during a pregnancy from pre-existing endometriosis are very rare.

It is understandable that ovarian function, particularly estrogen production, would be considered a major factor in the growth of this disease; for at least 35 years removal of all ovarian tissue or irradiation castration has been an accepted, though radical, form of treatment. The increasing incidence of symptomatic growth with the delay in childbearing and the salutary effects of pregnancy have not been as easy to explain.

The individual variabilities in growth of external endometriosis have been confusing. Many women have clinical evidence of endometriosis, for example, nodules in the cul-de-sac, which are relatively free of symptoms and which stagnate for years; conservative observation through the menopause is our hoped for and frequently realized plan. Other women have extremely rapid growth of the process, with or without increasing symptoms, over the course of a few months or a year. These peculiar patterns of growth, the frequent lack of correlation between symptoms and the extent of the involvement, and the common absence of histologic proof have made clinical treatment programs extremely difficult to evaluate.

The role of progesterone and its intermittent withdrawal has received very little consideration in most of the work done on external endometriosis. Despite extensive pelvic and ovarian involvement, the ovaries continue to function remarkably well and generally produce sufficient estrogen and *progesterone.* Abnormal uterine bleeding secondary to ovarian dysfunction from the presence of external endometriosis is not as frequent as most of the textbooks would lead us to believe; in a clinical group of 516 patients with external endometriosis Scott and Te Linde[5] felt that not more than 14 to 20 per cent had abnormal uterine bleeding which could be specifically related to the influence of this disease.

The hormonal influences which result in normal menstruation are essentially the withdrawal of the intermittently produced progesterone from an estrogen-primed endometrium. The amazing growth potential of endometrium is self-evident from observations on the rapidity of endometrial repair and growth following menstruation. Moore[3] has recently demonstrated this remarkable growth in tissue culture. The ectopic areas of endometrial tissue can be considered "miniature uteri," for they are composed of endometrial glands and stroma, surrounded by a variable amount of connective tissue and smooth muscle. These "miniature uteri" under average conditions should be subjected to the same circulating hormones as is the normally located endometrium. If the ectopic endometrial tissue has not become too fibrotically encased or too cystically

compressed or degenerated, it should be a healthy estrogen-primed endometrium which would respond to progesterone and progesterone withdrawal by "menstruating" into the adjacent tissues.

We, with Te Linde,[6, 10] in previous work with rhesus monkeys, demonstrated the probable viability of the menstrually shed fragments of endometrium and in addition that the presence of peritoneum was not essential for the implantation and growth of these fragments. Therefore, fragments of ectopic endometrium, shed at the time of progesterone withdrawal, could spread locally into adjacent tissues and tissue planes, again become implanted, and grow. In accord with our previous experimental findings and from the work of Javert,[1] lymphatic spread of the ectopic endometrial fragments would be quite feasible.

The present experiments on rhesus monkeys were undertaken to test this hypothesis, i.e., that the growth of external endometriosis is primarily dependent upon intermittent progesterone withdrawal from an estrogen-stimulated ectopic endometrium. Certainly the experimental transplants of endometrium in the majority of the castrated animals were grossly much larger in the group which received estrogen plus intermittent progesterone than in the groups with constant estrogen and constant progesterone, constant estrogen or no exogenous hormones. In at least one animal in each of the groups receiving hormones evidence of old or recent hemorrhage in the transplants could be correlated with the presence of bleeding from the uterus. The gross and microscopic extent of the hemorrhage was much greater in the group receiving constant estrogen and intermittent progesterone.

It should be noted that the present authors[7] have reported on the use of large doses of diethylstilbestrol in experimental endometriosis of the rhesus monkeys and that in 3 of the 4 animals hemorrhage in the external endometriosis could be correlated with the presence of bleeding from the vagina. It is postulated that any combination of estrogen and progesterone or estrogen alone which can cause desquamation of the normally located endometrium could cause desquamation of the endometrium within areas of external endometriosis. However, clinical experiences with estrogens to inhibit ovulation in patients with external endometriosis have shown that pain is usually relieved, even though estrogen-induced uterine bleeding occurs.

There was no widespread dissemination of the endometriosis in any of these animals. It is likely that repeated episodes of retrograde (tubal) transport of endometrial fragments is a more important factor in explaining extremely rapid pelvic spread of the disease than extension or transport from local growths already present.

It was stated that fibrotic encasement or cystic compression or degeneration of the ectopic endometrium might prevent it from receiving the full impact of the circulating hormones and thus allow it to stagnate temporarily or permanently. Experimental proof of these statements would be difficult. The cystic compression or degeneration of endometrium within the wall of a large "chocolate cyst" of the ovary could make this tissue nonvisible and explain why we

seldom see operative dissemination of endometriosis into the pelvis or the abdominal incision at the time of surgery, even though rupture with spillage is the rule and not the exception. Fibrotic encasement is probably the protective mechanism whereby the host tissues wall off the endometrium as though it were a foreign body and then ultimately make it inaccessible to the full influences of the circulating hormones. Sturgis[9] believes that this walling-off process is fundamentally responsible for the pain in endometriosis.

Delayed childbearing amounts to repeated and uninterrupted episodes of progesterone withdrawal from an estrogen-primed endometrium. If retrograde menstruation is a major factor and the fragments of endometrium which are shed are viable, then the longer pregnancy is delayed the greater will be the possibility of the development of external endometriosis. Since the levels of estrogen and progesterone are constantly elevated during pregnancy and there are no episodes of progesterone withdrawal, it can be reasoned that hemorrhage into the ectopic endometrium does not occur and the process stagnates.

Uninterrupted episodes of progesterone withdrawal from estrogen-stimulated external endometriosis can be one important factor in its growth and possible spread, provided the endometrium in these areas is not too fibrotically encased or cystically compressed and degenerated to receive the full influence of these hormonal changes. In addition, repeated normal menses could result in more episodes of transtubal shedding of endometrial fragments and thereby become another important factor in the growth and spread.

Although the female rhesus monkey is a cyclically menstruating primate with patent uterotubal junctions, care must be exercised in transferring experimental studies in this animal to the performance of the human female. Progesterone metabolism and the secretory endometrial response to progesterone[2] have some minor differences in the monkey and the human female.

Summary and Conclusions

1. External endometriosis has the following clinical peculiarities: (1) As a benign condition, it is limited in its clinical manifestations to the years of menstrual function. (2) It has not been identified as a disease entity prior to the menarche and postmenopausally it becomes atrophic and asymptomatic. (3) Delayed childbearing and several years without a pregnancy predispose to its prevalence and probably its growth. (4) Pregnancy has a salutary effect upon the disease. During pregnancy symptoms are relieved and the disease becomes essentially quiescent.

2. Normal menstruation occurs as a result of progesterone withdrawal from an estrogen-primed endometrium. Consider the areas of ectopic endometrium as "miniature uteri." If these areas of ectopic endometrium are not too fibrotically encased or cystically compressed or degenerated, they should react in a similar fashion to the circulating hormones.

3. Growth in ectopic endometrium could therefore be a manifestation of progesterone withdrawal from estrogen-stimulated endometrium, with desquamation, spread through fascial planes, and reimplantation of this desquamated endometrium. Lymphatic dissemination might also occur at this time.

4. Reimplantation and growth of this desquamated ectopic endometrium are surmised from the experimental evidence that menstrually shed endometrium is probably viable.

5. Rhesus monkeys were castrated, surgically excised endometrium was transplanted to four areas (three pelvic and one abdominal wall), and the transplants were observed grossly and microscopically for up to 37 months. The animals were divided into the following study groups: I, no hormones; II, constant estrogen; III, constant estrogen and constant progesterone; IV, constant estrogen and intermittent progesterone.

6. The transplants were studied periodically by exploratory labarotomy and biopsy.

7. The results were not entirely uniform but the major gross evidence of local growth occurred in the group which received constant estrogen and intermittent progesterone. Two animals which received no hormones showed evidence of viability of the transplants and one animal that received estrogen alone showed endometrial hyperplasia in the external endometriosis. In all of the groups which received hormones there was a rough correlation between the presence of uterine bleeding and evidence of bleeding in the endometrial transplants.

8. The additional growth in the animals which received estrogen and intermittent progesterone was local and not disseminated. It is postulated that disseminated growth may be primarily a result of repeated episodes of transtubal (retrograde) menstruation from the parent endometrium.

9. Enveloping and encasement fibrosis is considered a host reaction to the presence of ectopic endometrium and its periodic "menstruation." Once this process reaches its ultimate aim the ectopic endometrium stagnates because the full amount of circulating hormones is no longer locally available.

10. Care must be exercised in transferring results from experiments with rhesus monkeys to human performance.

We wish to express our appreciation to the former director, Dr. George W. Corner, and the present director, Dr. James D. Ebert, for their cooperation in this study and for the use of their facilities at the Carnegie Institution of Washington, Department of Embryology, Baltimore, Md.

References

1. Javert, Carl T.: AM. J. OBST. & GYNEC. **62**: 477, 1951.
2. Krohn, P. L.: J. Endocrinol. **12**: 69, 1955.
3. Moore, J. G.: Fertil. & Steril. **7**: 411, 1956.
4. Scott, R. B.: AM. J. OBST. & GYNEC. **47**: 608, 1944.
5. Scott, R. B., and Te Linde, R. W.: Ann. Surg. **131**: 697, 1950.
6. Scott, R. B., Te Linde, R. W., and Wharton, L. R., Jr.: AM. J. OBST. & GYNEC. **66**: 1082, 1953.
7. Scott, R. B., and Wharton, L. R., Jr.: AM. J. OBST. & GYNEC. **69**: 573, 1955.
8. Scott, R. B., and Te Linde, R. W.: Obst. & Gynec. **4**: 502, 1954.
9. Sturgis, S. H., and Call, B. J.: AM. J. OBST. & GYNEC. **68**: 1421, 1954.
10. Te Linde, R. W., and Scott, R. B.: AM. J. OBST. & GYNEC. **60**: 1147, 1950.

Discussion

DR. H. HUDNALL WARE, JR., Richmond, Va.—It is interesting to note that the endometrial transplants lived in 2 of the Group I animals without exogenous hormones. The

results obtained in the group of monkeys receiving constant estrogen and intermittent progesterone certainly appear to be sufficient to prove that this combination will stimulate the growth of endometrial tissue transplanted outside the normal uterine site. The presence in many nodules of active endometriosis with local spread by infiltration in transplanted tissue is proof of the ability of the transplants to continue normal function in tissues outside the uterus under certain types of stimulation.

I wish to ask Dr. Scott if he thinks prolonged treatment with estrone and progesterone to stimulate menstruation in young women with irregular menses may increase the incidence of endometriosis in some of these patients?

DR. CARL T. JAVERT, New York, N. Y.—Having had no experience with the hormone treatment of endometriosis in either the human or the monkey obviously qualifies me to speak on the subject.

Drs. Scott and Wharton have continued their brilliant experimental work on endometriosis in the monkey by studying the effects of estrogen and progesterone treatment on castrated animals. Their results are well within the bounds of expectation, namely, that estrogen alone did not suppress the endometrial transplants but maintained in them a proliferative pattern, while hyperplasia occurred in one monkey. Dr. Scott also employed a well-recognized concept that progesterone withdrawal in an estrogen-stimulated endometrium causes bleeding. He found that constant estrogen and intermittent progesterone treatment caused the endometrial transplants to grow and bleed. The latter could be correlated with uterine bleeding.

At a Symposium on Endometriosis in January at the New York Academy of Medicine, Dr. Scott was the moderator and Dr. Hellman discussed the hormone therapy of endometriosis. He referred to the work of Wilson with testosterone and the work of Karnaky with stilbestrol. At that time I raised the question regarding chorionic gonadotropic hormone since it is generally accepted that pregnancy has a salutary effect on endometriosis, as Dr. Scott has mentioned. It inhibits the cyclical changes of the endometrium lining the uterus and I suppose of the heterotopic areas as well. May I ask Dr. Scott if he has studied the effects of this hormone on the monkey? Another question I wish to ask is relative to the 5 monkeys that died of tuberculosis. Were they in the treated or untreated group? Can he tell us whether stilbestrol causes increased fibrosis in the lesions of tuberculosis?

In closing may I ask a final question: What does he think of the theory of celomic metaplasia in the light of his experimental studies on endometriosis? I believe it is time for us to recognize that this theory has only historical interest.

DR. RONALD R. GREENE, Chicago, Ill.—I wish to ask Dr. Scott some questions.

1. It was implied that in ectopic endometrium, including endometriomas, there would be endometrial stroma, glands, and musculature. Do you find development of muscularis in endometriomas?

2. The effect of constant stimulation with estrogens over a long period of time in the monkey is apparently somewhat dissimilar to the findings in the human. My memory has failed me this morning, but there have been some very good studies by Dr. Laman Gray in which he did serial biopsies of the endometrium of patients on constant stilbestrol and got an atrophic condition in the endometrium. We have done a similar experiment. We never attained atrophy of the endometrium but certainly it became very inactive and could be classified not as active hyperplasia but as regressive hyperplasia, if you will. Dr. Scott's remark about the showering of desquamated endometrium in the tube is a lovely postulation.

DR. JEAN P. PRATT, Detroit, Mich.—Mention was made of the rapid growth of endometriosis for about 3 to 7 months. From time to time statements are made about the rapid clinical growth of endometriosis in the patient. I have looked and looked for that growth but seldom am able to find it. I wonder if that is my own experience or a general one. It

seems to me that, by the time you detect it, what has happened has happened and it does not increase during the time of observation. Does that apply to the human as well as the animal?

DR. CURTIS J. LUND, Rochester, N. Y.—I wish to ask a question. With the prolonged treatment with progesterone and estrogen, did you observe the decidual reaction of pregnancy?

DR. SCOTT (Closing).—Dr. Ware wonders if our cyclical hormone treatment of patients with abnormal uterine bleeding or with amenorrhea might predispose those individuals to endometriosis. I believe any hormone combination which will allow endometrial shedding will predispose to endometriosis. The fact that a woman is born with a potential of cyclical menstrual flow and patent uterotubal junctions predisposes her to external endometriosis, and if we adjust our hormone treatment to mimic the normal relationships she is capable of developing external endometriosis.

I have not had experience with gonadotropic substances experimentally but would like to try it. I shall let Dr. Javert know what we find. I doubt that it has much influence. The reason external endometriosis is quiescent during pregnancy is that there are constant levels of estrogen and progesterone, no intermittent withdrawal.

As for the animals with tuberculosis, we did not notice an increase in the fibroblastic reaction about the areas of ectopic endometrium. Dr. Javert is making me stick my neck out and I might as well do just this. Everyone gets enthusiastic about something and may go off the deep end a little. Of all the possible theories of endometriosis, the least likely is the celomic metaplasia theory, and I believe that we may bury this theory before long.

Dr. Greene asked about smooth muscle in the ovary. There are smooth muscle fibers. We have shown this about endometriosis in the ovary by differential staining technique. It may come from smooth muscle in vessel walls.

Atrophy of endometriosis with prolonged estrogen therapy might be possible, but in such a case I would like to know what all the tissue shows microscopically. When I look at one biopsy area that only tells me about that particular area but not what is deeper. Dr. Laman Gray reported upon a patient who was treated with large doses of estrogen for endometriosis over a period of one year. He had some excellent histologic studies from the completely excised nodules. There was a remarkable amount of hyperplasia that developed under such treatment.

I am in agreement with Dr. Pratt that in the vast majority of instances rapid clinical growth is seldom seen. We all have found uterosacral nodules which gave no symptoms and did not grow, but we do have the occasional patient who very suddenly develops severe and extreme symptoms. It is not common.

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MALIGNANT NEOPLASIA IN THE ENDOMETRIUM*

A Ten-Year Experience in Private Practice

JOHN A. WALL, M.D., AND RENÉ MASTROVITO, A.B.,
HOUSTON, TEXAS

(From the Department of Obstetrics and Gynecology, Baylor University College of Medicine, and the Department of Gynecology, Methodist Hospital)

THE natural history of cancer developing in different anatomic sites presents an inexhaustable source for study. Endometrial cancer often reveals physiologic relationships of particular interest from the standpoint of endocrinology and etiology. Obesity, sterility, hypertension, diabetes, and hirsutism are noted for their frequent association with endometrial carcinoma.

The present study serves to corroborate these findings and may add somewhat to the growing knowledge regarding the endocrine status of these patients. The series is of interest from the standpoint that the entire responsibility for most of these patients has been in the hands of one man during treatment and follow-up. In some instances, patients seen in private practice have earlier diagnoses than those referred to clinics and thus may derive a better chance for definitive treatment and consequent improvement in prognosis.

Diagnosis

For many years an attempt has been made to attain early diagnosis by simple endometrial biopsy. In the present series, 29, or 41 per cent of the 70 cases, were diagnosed by this means. Endometrial biopsy is employed routinely in the office on patients who have irregular bleeding and who are candidates for diagnostic curettage. The procedure requires but a few minutes and causes little pain. We have employed no anesthesia, but Burch[5] reports that he has successfully employed a topical anesthesia applied with a cotton swab.

It is often difficult to convince a woman that curettage is necessary when her only complaint is irregular vaginal bleeding. Many of these women are used to varying degrees of menstrual irregularity and the possible significance of bleeding will often be ignored. In a former series reported by the senior author,[61] when negative biopsies were returned and a diagnostic curettage recommended, 36 per cent failed to comply with the advice.

Whenever endometrial biopsy is negative, diagnostic curettage is imperative. The endometrial biopsy is adequate only when it is positive and totally inadequate when it is negative. Its greatest value lies in the fact that it makes diagnosis possible at an earlier date and therefore may favorably affect the prognosis. In our experience, there have been no infections and no cause to suspect dissemination of tumor.

When adenocarcinoma is reported on tissue removed from the cervix, one should suspect endometrial carcinoma which has extended downward from the fundus. Although primary adenocarcinoma of the cervix has been claimed to

*Presented at the Eightieth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 27-29, 1957.

occur in a ratio of 3 to 5 per cent, in our experience it has been much less frequent. Thus, a further benefit from the use of endometrial biopsy is the discovery of unsuspected *corporis et colli* lesions, enabling a corresponding change in therapy.

Present Material—70 Cases

After diagnosis of carcinoma of the endometrium, treatment is instituted in accordance with individual circumstances. Treatment in this series was in accord with that followed in many clinics. The therapy which we have considered preferable, and try to standardize whenever applicable, consists of 2 radium implantations approximately 3 weeks apart, with the use of the Heyman technique of multiple intrauterine radium sources, with modification using vaginal radium and the dosage tables worked out by Fletcher.[15] The time element between the first and second radium insertion is chosen in the hope that there may be some sloughing of the tumor inside the uterus in order that the second radium implantation may more closely approximate the tumor base. Four weeks following the second radium treatment, total abdominal hysterectomy and bilateral salpingo-oophorectomy are performed.

In patients with *corporis et colli* lesions, irradiation is directed to the cervix, the paracervical triangle, and the vagina. After this, radical hysterectomy with bilateral lymphadenectomy is performed if technically feasible. This radical procedure is undertaken only when the cervix is involved.

A systematic distribution of radium is utilized in the Heyman technique. The primary irradiation is accomplished by multiple radium sources packed within the uterine cavity. In about half the patients in this series, a cervical tandem containing 15 mg. of radium was used in addition to the multiple capsules. Radiation is delivered to the vagina, particularly the vault, by means of vaginal ovoids in the first application and a vaginal cylinder in the second. This radium pattern is used to deliver an average dose of 2,400 gamma r to a spheroidal area 2 cm. below the endometrium. The vaginal applicators are designed to deliver 3,000 gamma r to the vaginal mucosa in each application. The vaginal ovoids and cylinders are loaded and the time adjusted for each in order that the desired vaginal and uterine doses will be delivered according to this predetermined plan.

Although in some instances an additional cervical tandem was used, this radium was omitted from the calculations for the sake of simplicity. We have calculated that the tandem's contribution will never be more than 5 per cent of the average dose from the Heyman capsules.[23] Although we express radiation to the uterus in terms of average intensity, the region of greatest effect is that closest to the central mass of Heyman capsules, while the regions of lowest intensity are the fundus and the cervix. The cervical tandem tends to prevent this drop in dosage gradient at the cervical area.

In this series, the actual dose delivered was calculated for 31 patients, 21 of whom were found to have no residual tumor in the surgically removed uterus. The average dose delivered to the patients who had no residual tumor was 4,200 gamma r in 2 applications, whereas the average dose delivered to those who had tumor residue was 3,590 gamma r to a surface 2 cm. below the endometrium. Consequently, we made an effort to examine the reasons for the lower amounts of irradiation received by the patients who had residual cancer.

Analyzing the therapy administered to these patients, we found that modification of the therapeutic technique was often required. Frequent contraindications to surgery are present, for women differ externally, internally, and eternally. Some are forbiddingly obese, while others present a surgical problem because of intercurrent cardiovascular disease. In these instances, irradiation is administered for palliation, and sometimes it has resulted in lifelong control of the endometrial cancer.

Of the 70 patients in this series, 14 had radium but no surgery by the author, 7 had surgery with no preoperative radium, and 49 had the combined therapy of preoperative radium followed by hysterectomy (Table I).

TABLE I. RADIATION THERAPY WITHOUT SURGERY BY AUTHOR

Subsequent surgery elsewhere	6
Poor surgical risks or disease too advanced	6
Postoperative irradiation	2
Total	14

Of the 7 who had surgery with no preoperative radium, 2 were treated some 10 years ago before we adopted the Heyman technique. Four had postoperative irradiation and one case was diagnosed following operation for a supposedly benign condition (Table II).

TABLE II. SURGERY WITHOUT PREOPERATIVE IRRADIATION

Treated before author began Heyman technique	2
Postoperative irradiation	4
Diagnosed postoperatively, no irradiation	1
Total	7

The 49 patients who had combined therapy include all who had had any preoperative radium, regardless of amount. Following hysterectomy, it was found that there were 19 positive and 30 negative uteri, i.e., 61 per cent with no residual tumor.

Further study of these 49 patients who had combined therapy indicated that 21 had had less than optimal radium, or unknown amounts delivered by other therapists. Of these, 6 had been irradiated elsewhere, 6 had had only one radium treatment, 5 had uteri too small to accommodate adequate amounts of radium, and 3 had *corporis et colli* lesions. One had a double uterus, double cervix, and septate vagina (Table III).

TABLE III. COMBINED THERAPY

Less Than Optimal or Unknown Irradiation.—		
Irradiation therapy elsewhere	6	
Only one radium treatment	6	
Uteri too small	5	
Corporis et colli lesions	3	
Double uterus	1	
		21
Optimal Therapy.—		
Negative uteri	24	
Residual tumor	4	
		28

The 28 remaining each had optimal therapy consisting of 2 preoperative radium implantations followed by total abdominal hysterectomy. Four of the 28 had residual tumor and 24 had negative uteri. Thus, 86 per cent of those who had adequate radium therapy showed no residual cancer in the uterus. The pathologist reported 2 of the 4 cases deemed positive as questionable and one as inactive (Table III).

The prognostic significance of a uterus with no residual tumor has been discussed by others. In a series of 91 patients who had undergone preoperative irradiation followed by hysterectomy, Sherman and Arneson[48] found that 81 per cent survived 5 years. Further evidence of the salvage achieved with combined therapy is offered in a table compiled by Kimbrough[28] showing end results in 460 patients from the literature with a 5 year survival of 70 per cent.

Time has been too short for evaluation of the benefits derived from the vaginal irradiation but it is possible that this could represent the most significant contribution of preoperative radium by virtue of the prophylaxis administered to the submucosal lymphatics.

Points of Special Interest

The endocrinopathic anomalies found in this series deserve special mention because they were numerous and often extraordinary. Fourteen of the patients, or 20 per cent, weighed over 200 pounds. Six were very tall and raw boned in stature, although the average height was 5 feet, 5 inches. When correlated with average weight for women in this age bracket, those in this series were about 10 pounds heavier than average. Seventeen, or 24 per cent, were married and nulliparous and 21, or 30 per cent, had hypertension or some cardiac complication. Nine, or 13 per cent, had high blood sugar. However, only 2 of these were on insulin, and the fluctuating glycosuria in the others was controlled by diet (Table IV).

TABLE IV. ENDOCRINE ABNORMALITIES

	NO. OF PATIENTS	%
Weight over 200 pounds	14	20
Menopause after age 50	26	37
Nulliparity	17	24
Hypertension of cardiopathy	21	30
Transient glycosuria	7	10
True diabetes	2	3

The age at onset of the menopause was generally normal, averaging 46 years. However, there were 26, or 37 per cent, who underwent the menopause after the age of 50. The average age at onset of the menopause was considerably lowered by the fact that one patient was only 32 years old when seen, while 3 others had ceased menstruating 35, 28, and 18 years prior to the development of endometrial carcinoma. We were able to confirm that one had been castrated surgically 35 years preceding the diagnosis of endometrial carcinoma through a report from the clinic where bilateral oophorectomy had been performed.

Six had had unknown amounts of irradiation some years before the development of endometrial carcinoma and many reported that they had taken hormones. Significant conclusions with regard to previous irradiation or previous endocrine therapy could not be reached, however.

Of singular interest are those patients who, according to pathologic reports, developed 2 or more primary neoplasms. In one patient primary breast cancer and basal-cell carcinoma of the lip were followed by endometrial carcinoma two years later (Table V).

TABLE V. PRIMARY TUMORS IN ADDITION TO ENDOMETRIAL CARCINOMA

	NO. OF PATIENTS
Malignant.—	
Breast cancer	2
Pseudomucinous cystadenoma of ovary	1
Meningiosarcoma of brain	1
Bronchogenic carcinoma	1
Total	5
Benign.—	
Bilateral multiple bronchial adenomas	1
Pituitary chromophobe adenoma	2
Total	3

A second patient underwent hysterectomy for endometrial carcinoma in 1950. Two years later, she had a radical mastectomy for primary breast cancer. She is living and well at present, 7 years following the first operation.

A third patient had a pseudomucinous cystadenocarcinoma of the ovary discovered following hysterectomy for endometrial cancer.

A fourth was treated for endometrial carcinoma in 1952 and died of meningiosarcoma of the brain in 1957. Autopsy established no evidence of endometrial cancer.

A fifth patient was treated for endometrial carcinoma in 1951 and 3 years later developed bronchogenic carcinoma of the lung which proved fatal. Autopsy showed no trace of endometrial carcinoma.

A sixth patient was treated for adenocarcinoma of the endometrium and 8 years later developed multiple benign bronchial adenomas.

Two patients in this series had chromophobe adenomas of the pituitary. Both were blind and both weighed over 240 pounds.

The first of these, Mrs. I. R., was a 62-year-old woman who had undergone resection of the right cystic ovary and bilateral salpingectomy in 1922. In 1930 she underwent surgery for a pituitary tumor, which recurred 10 years later. In 1948, she consulted the author with the complaint of 3 years' uncontrolled vaginal bleeding. Diagnostic curettage and radium implantation were performed. The pathologic reports showed no evidence of malignancy, but endometrial hyperplasia decidedly abnormal for a postmenopausal woman. A second curettage the following year yielded a similar diagnosis. Following this, she returned to her home, but her bleeding remained unabated. One physician later reported that he had administered massive doses of stilbestrol, but it would be impossible to determine what medication she actually had, since her husband was a druggist who also prescribed resolutely on her behalf. In 1954, 6 years after she was seen by the author, she developed adenocarcinoma of the endometrium and was treated by radium elsewhere. She died in 1955 without hysterectomy. Autopsy was not performed (Table VI).

TABLE VI. MRS. I. R., BLIND, AGED 62 (IN 1948), WEIGHT 243 POUNDS, 5 FEET, 7 INCHES TALL

YEAR	PROCEDURE	DIAGNOSIS
1922	Resection of cystic ovary	
1930	Operation for pituitary chromophobe adenoma	
1948	Curettage, radium implantation (4,380 mg. hr.)	Endometrial hyperplasia
1949	Curettage	Endometrial hyperplasia
1954	Curettage	Adenocarcinoma of the endometrium

TABLE VII. MRS. G. G., BLIND, AGED 63 (IN 1953), WEIGHT 245 POUNDS, 5 FEET, 9 INCHES TALL

DATE	PROCEDURE	DIAGNOSIS
February, 1953	Curettage, radium implantation	Adenocarcinoma of the endometrium
June, 1955	Diabetes developed	
Dec. 1, 1955	Autopsy	Pituitary chromophobe adenoma Pancreatic necrosis Adrenal hyperplasia (79 grams) Moderate cellular stroma of ovaries

The second patient with pituitary disease was also blind and obese, weighing 245 pounds. She had hypertension and hirsutism, and presented the buffalo hump characteristic of Cushing's syndrome. Following the diagnosis in 1953 of adenocarcinoma of the endometrium, she was treated by 2 radium implantations of multiple intrauterine sources. Operation was not performed because of her physical handicaps. She lived for 2 years following this treatment but died after developing diabetes during the last 6 months. Autopsy indicated that death was caused by necrosis of the pancreas. It also revealed chromophobe adenoma

of the pituitary and extreme hyperplasia of the adrenals. She had a total of 79 grams of adrenal tissue, as contrasted with the normal high of 15 grams. There was no residual tumor in the uterus, but metastatic carcinoma was found in the liver (Table VII).

Endocrinologic Studies

For many years, there has been an attempt to correlate endocrine status with the development of adenocarcinoma of the endometrium. Variations in the qualitative and quantitative relationship of estrogen and progesterone may be indicated by inference. As far back as 1935, Stein and Leventhal[54] described a phenomenon occurring in relatively young women combining menstrual irregularities, obesity, sterility, and hirsutism. They observed that these women were more prone to develop endometrial carcinoma than could be explained on the basis of chance. They surmised that there was some abnormality in the pituitary-ovarian-adrenal balance operating in these patients. Following this, other investigators[24] began seeking the polycystic ovaries with thick cortical rinds, as well as the clinical manifestations of the Stein-Leventhal syndrome.

In 1949, Sturgis, Hertig, and Bengloff[50] conducted a survey of young women with endometrial carcinoma and found 4 with the thick-walled, polycystic ovaries. The appearance of these ovaries reminded them of certain studies in animals in which induced Cushing's syndrome in dogs had been accompanied by hyperplasia of the ovarian cortices. They noted that in women with Cushing's syndrome the ovaries show overgrowth of the cortical stroma. Furthermore, they observed that cases of "Stein-Leventhal syndrome or endometrial carcinoma in youth frequently resemble incomplete forms of Cushing's syndrome."

Of further interest is Hertig's[19] theory that when massive doses of estrogens are withdrawn, the response may be excessive activity of the anterior pituitary, with added reaction from the adrenal. He noted, "since estrogen withdrawal in the menstrual cycle stimulates anterior pituitary activity, the waning of excess estrogen in post-menopausal women may be expected to do likewise."

In 1951, Dockerty and associates[14] reviewed the histories of 1,694 patients with corpus cancer and discovered 36 who exhibited the clinical manifestations of the Stein-Leventhal syndrome.

In the current year, Jackson and Dockerty[24] again reviewed a large series seeking additional patients with these characteristics. The search produced 43 patients who showed 3 of the recognized criteria. Sixteen of the 43 also had carcinoma of the endometrium. The authors state, "it is considered that endometrial carcinoma is best recognized as a late complication of the unsuccessfully treated syndrome."

Pathologic examination of the ovaries of the patients with endometrial carcinoma disclosed that in 9 there were hilar cell rests consisting of Sertoli-like or Leydig-like cells. Other investigators have observed hilar rests of cells which simulate these testicular elements in the ovaries of women with hyperplasia of the endometrium. In our series, review of the pathologic reports failed to disclose this type of ovarian pathology.

Whereas some pathologists have observed hilar cell changes and ovarian stromal hyperplasia in patients with endometrial carcinoma, routine pathologic reports following hysterectomy usually fail to note changes of this nature. This does not necessarily mean that such changes were absent, but only that their possible significance may not have been appreciated. It may be that further review of existing slides would disclose more examples. If other investigators would survey their available material, considerable light might be thrown on the vague and sometimes contradictory endocrine status of patients with endometrial carcinoma. Further evidence may be found in retrospect and the body of knowledge expanded. Women who develop endometrial cancer late in life often

demonstrate 1 or 2 of the typical endocrine anomalies such as obesity, sterility, diabetes, and hirsutism, while those who develop the disease early in life tend to show 3 or more. This strongly suggests that an endocrine imbalance of greater severity was present in the younger group, and might also account for the fact that they developed endometrial carcinoma at such an early age.

Conclusion

In conclusion it is well to recall that our best therapeutic efforts still fall short of ultimate victory. Advance in the attack on cancer is not necessarily to be achieved through improved therapeutics, but perhaps may come through a better understanding of the physiologic and biologic interrelationships. It may be that more extensive studies in endocrinology will one day yield significant truths regarding the body's defenses against malignant diseases.

If endocrine imbalance is involved in the etiology of endometrial cancer, studies which will aid in the attainment of endocrinologic homeostasis may eventually prove of greater value than any therapeutic approach in use today. To this end, the physician must be ever alert to laboratory research and new discoveries in the fields of chemotherapy and preventive medicine. Through a recognition of characteristic endocrine manifestations, we may come to identify the "cancer prone" individual, as industry now recognizes the "accident prone," and takes preventive measures on their behalf. In the management of adenocarcinoma of the endometrium, particularly, early recognition of the significance of endocrinopathy such as the Stein-Leventhal syndrome may justify prophylactic measures, that certain women may be spared the inevitable development of cancer of the endometrium.

Summary

A study has been conducted of approximately 70 patients with adenocarcinoma of the endometrium treated by one physician in private practice over a 10 year period.

Special attention has been given to the high preponderance of endocrine stigmas found among patients in this series. Accompanying tables show the incidence of diabetes, aberrations of weight and stature, concurrent breast disease, and other glandular irregularities. Two patients had chromophobe adenoma of the pituitary.

The value of endometrial biopsy as a means of immediate diagnosis is stressed.

The treatment of carcinoma of the corpus uteri includes 2 preoperative radium implantations by the Heyman packing method, followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. Individual considerations, such as age, obesity, or heart disease often necessitate modifications. Improved dosimetry has made possible precise measurements of the amount of radiation delivered to a given area. Dosages are calculated showing the results obtained when optimal radiation was employed.

Although insufficient time has elapsed for 5 year results in the entire series, a tentative evaluation is made from studying the pathologic reports following operation. The prognostic significance of the presence or absence of residual tumor in the uterus is discussed.

References

1. Arneson, A. N.: Bull. New York Acad. Med. **29**: 395, 1953.
2. Arneson, A. N., Stanbro, W. W., and Nolan, J. F.: AM. J. OBST. & GYNEC. **55**: 64, 1948.
3. Bourne, H. B., et al.: Surg., Gynec. & Obst. **101**: 753, 1955.
4. Brunschwig, A., and Murphy, A.: AM. J. OBST. & GYNEC. **68**: 1482, 1954.
5. Burch, J. C.: CA **6**: 203, 1956.
6. Burch, J. C., and Klinger, H. H.: J. Tennessee M. A. **25**: 142, 1932.
7. Corscaden, J. A.: Gynecologic Cancer, ed. 2, Baltimore, 1956, Williams & Wilkins Company.
8. Corscaden, J. A., and Gusberg, S. B.: AM. J. OBST. & GYNEC. **53**: 419, 1947.
9. Corscaden, J. A., and Tovell, H. M.: AM. J. OBST. & GYNEC. **68**: 737, 1954.
10. Cosbie, W. B., et al.: AM. J. OBST. & GYNEC. **67**: 1014, 1954.
11. Costolow, W. E., et al.: Am. J. Roentgenol. **71**: 669, 1954.
12. Cron, R. S., et al.: AM. J. OBST. & GYNEC. **70**: 548, 1955.
13. DeVere, R. D., and Dempster, K. R.: J. Obst. & Gynaec. Brit. Emp. **60**: 865, 1953.
14. Dockerty, M. B., Lovelady, S. B., and Faust, G. T., Jr.: AM. J. OBST. & GYNEC. **61**: 966, 1951.
15. Fletcher, Gilbert H.: Personal communication.
16. Freed, J. H., and Pendergrass, E. P.: Am. J. Roentgenol. **71**: 253, 1954.
17. Gusberg, S. B., Moore, D. B., and Martin, F.: AM. J. OBST. & GYNEC. **68**: 1472, 1954.
18. Hecht, E. L.: AM. J. OBST. & GYNEC. **71**: 819, 1956.
19. Hertig, A. T., and Sommer, S. C.: Cancer **2**: 946, 1949.
20. Hertig, A. T., and Younge, P. A.: AM. J. OBST. & GYNEC. **64**: 807, 1952.
21. Heyman, J.: J. A. M. A. **135**: 412, 1947.
22. Heyman, J.: AM. J. OBST. & GYNEC. **69**: 502, 1955.
23. Heyman, J., and Benner, S.: Acta Radiol. **27**: 328, 1946.
24. Jackson, R. L., and Dockerty, M. B.: AM. J. OBST. & GYNEC. **73**: 161, 1957.
25. Jensen, A.: Acta radiol. **26**: 99, 1945.
26. Jensen, E. I., and Ostergaard, E.: AM. J. OBST. & GYNEC. **67**: 1094, 1954.
27. Klingler, H. H., and Burch, J. C.: J. A. M. A. **99**: 559, 1932.
28. Kimbrough, R. A.: S. Clin. North America **34**: 1685, 1954.
29. LeFevre, H.: Surg., Gynec. & Obst. **102**: 649, 1956.
30. Leucutia, T.: Am. J. Roentgenol. **68**: 770, 1952.
31. Loeffler, R. K.: Am. J. Roentgenol. **73**: 425, 1955.
32. Lewis, G. C., Jr., and Payne, F. M.: S. Clin. North America **34**: 1671, 1954.
33. Mansell, H., and Hertig, A. T.: Obst. & Gynec. **6**: 385, 1955.
34. McCartney, C. P.: S. Clin. North America **33**: 241, 1953.
35. McCartney, C. P., and Hayden, G. E.: Obst. & Gynec. **9**: 293, 1957.
36. McGarvey, R. N., and Gibson, W. E.: AM. J. OBST. & GYNEC. **63**: 836, 1952.
37. McKay, D. G., Hertig, A. T., and Hickey, W. F.: Obst. & Gynec. **1**: 125, 1953.
38. Novak, E.: J. A. M. A. **135**: 199, 1947.
39. Novak, E., and Mohler, D. I.: AM. J. OBST. & GYNEC. **65**: 1099, 1953.
40. Novak, E., and Rutledge, F.: AM. J. OBST. & GYNEC. **55**: 46, 1948.
41. Novak, E., and Yui, E.: AM. J. OBST. & GYNEC. **32**: 674, 1936.
42. Payne, F. L.: AM. J. OBST. & GYNEC. **34**: 762, 1937.
43. Sadler, J. M.: AM. J. OBST. & GYNEC. **70**: 17, 1955.
44. Scheffey, L. C., and Lang, W. R.: S. Clin. North America **32**: 1729, 1952.
45. Schmitz, H. E., and Gajewski, C. J.: S. Clin. North America **33**: 259, 1953.
46. Schmitz, H. E., Smith, C. J., and Gajewski, C. J.: AM. J. OBST. & GYNEC. **64**: 952, 1952.
47. Severinghaus, A. E.: J. Clin. Endocrinol. **4**: 583, 1944.
48. Sherman, A. I., and Arneson, A. N.: Am. J. M. Sc. **228**: 701, 1954.
49. Smith, G. V. S.: New England J. Med. **225**: 608, 1941.
50. Sturgis, S. C., Hertig, A. T., and Bengloff, H.: Cancer **2**: 957, 1949.
51. Speert, H.: Surg., Gynec. & Obst. **88**: 332, 1949.
52. Speert, H.: Cancer **1**: 584, 1948.
53. Speert, H.: AM. J. OBST. & GYNEC. **57**: 547, 1949.
54. Stein, I. F., and Leventhal, M. L.: AM. J. OBST. & GYNEC. **29**: 181, 1935.
55. Stewart, F. W.: Factors Influencing the Curability of Cancer, Proc. Third Natl. Cancer Conference, Philadelphia, 1957, J. B. Lippincott Company.
56. Stowe, L.: AM. J. OBST. & GYNEC. **51**: 57, 1946.
57. Swinton, N. W., Schwyzer, H. C., and Sass, R. E.: S. Clin. North America **34**: 791, 1954.
58. Te Linde, R. W., Jones, H. W., and Galvin, G. A.: AM. J. OBST. & GYNEC. **66**: 953, 1953.
59. Wall, J. A., and Bayoud, B. S.: South. M. J. **44**: 22, 1951.
60. Wall, J. A., and Klingensmith, W. R.: AM. J. OBST. & GYNEC. **59**: 901, 1950.
61. Wall, J. A., Fletcher, G. H., and MacDonald, E.: Am. J. Roentgenol. **71**: 95, 1954.
62. Way, S.: Malignant Disease of the Female Genital Tract, Philadelphia, 1951, The Blakiston Company.
63. Way, S.: J. Obst. & Gynaec. Brit. Emp. **61**: 46, 1954.

64. Way, S.: J. Obst. & Gynaec. Brit. Emp. 58: 558, 1951.
65. Woll, E., et al.: Am. J. Obst. & Gynec. 56: 617, 1948.

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Discussion

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pa.—In so far as diagnosis is concerned, there can be no disagreement with Dr. Wall's contention that a positive endometrial biopsy is not only valid but is also a saver of time and expense. On the other hand, no credence can be placed in a negative biopsy and, under these circumstances, diagnostic curettage becomes imperative.

The essayist has suggested at least two valuable additions to the radiation therapy which precedes definitive surgical treatment. The first of these is the repetition of the multiple source application of radium after an interval of 3 weeks, giving a total calculated radium dosage of 4,200 gamma r to a surface 2 cm. below the endometrium. Although this is quite under the dosage usually considered cancerocidal, its efficacy is attested by the fact that in 21 of 31 patients so treated no residual carcinoma could be demonstrated in the surgically removed uteri. Apparently this dosage caused no damage to surrounding structures in his patients. I wish to know whether symptoms referable to the bladder or rectum presented any problem.

The second thought-provoking suggestion is that of adding a cervical tandem and vaginal vault applicators to the intrauterine radium. This technique may well lessen the incidence of recurrences in the upper vagina.

In support of the concept of endocrine imbalance among patients with endometrial carcinoma the following report is presented. Dr. James Garnet in my department has studied the glucose tolerance of 50 of our patients with carcinoma of the endometrium and has controlled his findings by studying the glucose tolerance of 50 patients of comparable age who were known not to have this lesion. In the 50 patients with endometrial carcinoma, 31 had levels above normal, while only 10 of the 50 control patients presented this abnormality. The incidence of obesity and hypertension among our patients was similar to that reported by Dr. Wall.

Dr. Craig Muckle, who is a guest at this meeting, has collected from the literature the end results obtained by various authors following treatment by radiation alone, operation alone, and by a combination of radiation and subsequent hysterectomy. The 5 year survival among 2,122 patients treated by radiation alone was 48.8 per cent. The survival rate among 2,112 patients following hysterectomy alone was 57.8 per cent. The survival rate following combined treatment was 72.7 per cent. These statistics clearly indicate the superiority of combined therapy.

Sixty-one of our records were reviewed to determine the influence of residual carcinoma on 5 year survival. Among 41 who had residual carcinoma, 73.1 per cent survived for five or more years. Among 20 who had no residual carcinoma, 85 per cent survived 5 years.

With the increased effectiveness of the radiation therapy reported by Dr. Wall, long-term survival following combined therapy may be expected in more than 90 per cent of patients so treated.

DR. CHARLES E. McLENNAN, San Francisco, Calif.—I wish to ask for further clarification regarding two items related to diagnostic procedure. First, Dr. Wall performed endometrial biopsy routinely in his office and was able to detect about 40 per cent of his group of endometrial cancers in this fashion. Presumably the other 60 per cent were found after more extensive curettage of the uterus. Indeed, he considers curettage *imperative* whenever the biopsy does not yield carcinoma. But at the same time he points out that 36 per cent of the women who were advised to have curettages failed to heed the advice, and this suggests that quite possibly considerable numbers of endometrial cancers may have

been overlooked. One wonders what has become of these tumors and of the patients harboring them. I am particularly curious as to why curettage is so difficult to effect as a diagnostic procedure in the Houston area. We have met no serious resistance to it and have been inclined to perform it freely as part of the preliminary study of the patient with any degree of abnormal uterine bleeding or discharge, or with positive cytologic smears.

Second, Dr. Wall mentions the detection of endometrial cancer invading the cervix as a "further benefit from the use of endometrial biopsy." I recall having had appreciable difficulties deciding upon the precise origin of certain uterine adenocarcinomas, even after extensive exploration of the uterus under operating room conditions and after exhaustive histologic study of voluminous material. In view of these experiences, I am not clear as to how the endometrial biopsy curette has been helpful in localizing the primary site of an adenocarcinoma occupying more or less the entire extent of the uterine canal.

Regarding therapy, Dr. Wall advises two radium implantations 3 weeks apart, followed by hysterectomy a month later. He does not tell us what degree of success he has had with this so-called combined therapy, but he quotes statistics collected by others in support of the thesis that preoperative radiation generally is desirable. He says nothing, however, about the converse of the argument, although it is well known now that many clinical investigators —among them several members of this Society—have questioned the desirability of preliminary intrauterine irradiation for endometrial cancer. At the moment certainly there is no valid statistical evidence to support those who advocate preoperative radiation. It seems unlikely that this matter can be settled until the principle of random selection of patients for the rival methods of therapy has been applied to a suitably large series of cases, and I might suggest in passing that the necessary information could be accumulated within a very reasonable time by a cooperative group of investigators.

Lacking the initiative for such a large-scale venture in cancer therapy, we determined at Stanford a decade ago to embrace the then unpopular approach to endometrial carcinoma and to omit deliberately all preoperative radiotherapy. The ban on radium has been absolute, of course, in so far as our clinic service is concerned, but an occasional patient handled privately by a member of the faculty has had preoperative treatment. Recently we have surveyed our experience of the past 10 years and have included additional patients treated as early as 1940 in order to obtain for comparison a modest number treated by the combined method. In a group of 142 patients with endometrial cancer, there were 88 treated over 5 years ago and 82 per cent of these are alive today. More than 90 per cent of those treated by surgery alone or by radiation plus surgery have survived. Only half of those who had merely irradiation have lived more than 5 years. These results tend to strengthen a conclusion reached in 1945, after a review of material from the University of Minnesota Hospital, to the effect that hysterectomy is the essential item in the treatment of endometrial carcinoma and that the use of preoperative radium probably is an unnecessary gesture.

DR. HOWARD W. JONES, JR., Baltimore, Md.—Dr. Wall pointed out in his series the high incidence of obesity, hypertension, and diabetes. It will be recalled that Corscaden and Gusberg emphasized this same point a number of years ago and established what might be called a cancer habitus with respect to carcinoma of the body of the uterus. Furthermore, a number of investigators have commented on the possible background of estrogens in patients who develop carcinoma of the fundus. The work of Novak and Yui and of Howard Taylor, Jr., on the relation of endometrial hyperplasia to carcinoma of the fundus, the frequency of carcinoma of the fundus with the Stein-Leventhal syndrome, and the relationship of the stromal hyperplasia of the ovary to this lesion has a bearing on this point. We can therefore picture an obese patient with hypertension and diabetes and a background of estrogen administration as a likely candidate for this disease. And yet Dr. Masters advised us that the continuous postmenopausal administration of estrogens is helpful in preventing cardiovascular disease and diabetes.

This conflict cannot be resolved with the evidence at hand but resolved it must be before one can take a stand on the therapeutic desirability of routine postmenopausal estrogen therapy. The conflict is not one of the frustrating variety but is a conflict of

inadequate information. It is necessary to know, for instance, if patients who get carcinoma of the fundus have an increased amount of atherosclerosis, and to know whether the etiology of their hypertension and diabetes is of a different kind than that of the group spoken of by Dr. Masters. Although it seems to me that the results of the line of evidence developed by Dr. Masters are in conflict with the results of that developed by Dr. Wall and other investigators in this field, nevertheless such differences may in the end have proved not undesirable, for their resolution cannot help but give us a better understanding of the processes involved.

DR. AXEL N. ARNESON, St. Louis, Mo.—In assessing the value of preoperative irradiation, one must admit the possibility that radium applied in the vaginal vault may lessen the risk of recurrence in that region; that the so-called "devitalization" of tumor cells may lessen the risk of contamination at operation; and that the stenosing effects upon lymphatics may decrease the probability of dispersion at a later date. In my opinion, however, those factors are of lesser importance than the probability of total tumor control in explaining the gain in survival for the combined treatment.

It must be remembered that the principal evidence of improvement falls in the group of patients who show control of the tumor within the specimen removed at operation. The prognosis in those patients is of an order that exceeds 80 per cent. It is impossible to compare results upon a strictly uniform type of clinical material, but at that level of survival it is difficult to believe that more than 80 per cent of the patients present tumor strictly confined to the volume of tissue removed at operation. If all the tumor within the specimen shows control there may have been extensions within a narrow radius outside that volume also brought under control. There is no reason to expect that result among patients who show residual tumor that appears viable. Hysterectomy is the essential and definitive treatment because the biologic changes produced in the tumor are not known preoperatively.

It can thus be seen that degeneration of tumor within the uterus becomes an important aim. We do not yet understand the biophysical principles that will attain that result. It may depend upon qualities inherent within the tumor itself. There may be a dose factor and in that instance a time relationship. Due to the more rapid rate of administration, the contribution from radium can be more important biologically than that from x-rays, even at points outside the uterus. Dr. Wall has described a procedure in which two applications of radium are made, and he has emphasized certain time relationships in reference to both preoperative treatment and hysterectomy. I believe that to be important. We have generally employed a brief course of x-rays followed by a single application of radium. We have concluded that preoperative treatment is essential for patients who present enlarged uteri, and for those with undifferentiated tumors. We would like to attain a higher percentage of patients who show tumor control. Dr. Wall may have a better method. During the past 2 days, we have discussed time-dose relationships that might accomplish that effect. He may wish to comment upon that point but I believe he will agree that an answer is not available at this moment.

DR. SOMERS H. STURGIS, Boston, Mass.—I wish to comment in the same vein as Dr. Arneson on the time-dose relationship of radium and surgery. The important thing might seem to be to get the dose that will cut down the viability of cancer cells that may be squeezed out during surgery. Some years ago a study was made by Meigs and Jaffe of serial biopsies of cervical lesions after radium in regard to mitotic activity. They showed that 4 to 6 days after radium treatment there was a maximum reduction in mitotic activity. If mitoses can be considered an index of viability and transplantability, then it might seem that the usual time lapse of 4 to 6 weeks which Dr. Wall used, after radium treatment, might not be the best time to jump in with surgery because there usually is a recovery of mitotic activity after a few weeks.

Following this reasoning, some 4 or 5 years ago we started treatment of a series of endometrial cancers with one application of radium and then followed this by surgery in 7 to 9 days, hoping to take the tumor out at the time of least viability and thus cut down

recurrences, particularly in the vaginal vault. We have not had enough cases or long enough follow-up to know what the results will be, and this is only an extension of Dr. Arneson's comments.

I wish finally to ask Dr. Wall what recurrence he has had in the vaginal vault following his procedure.

DR. GEORGE KAMPERMAN, Detroit, Mich.—There seems to be a sharp controversy as to whether radiation should be combined with surgery. My experience with carcinoma of the endometrium is in both methods. This began in 1913 and for 20 years we operated upon patients with carcinoma as soon as the diagnosis was made. At that time our 5 year survival rate was 57 per cent. Since 1933 we have combined preoperative radiation with surgery and postoperative radiation, and we have a 5 year survival rate of 87 per cent. To me there is a big difference and it would be hard for me to want to give up the use of radiation as an adjunct to surgery. When I got the program and realized what Dr. Wall would be presenting, I looked up my own cases and I listed those on which I had operated myself. I found that 39 patients had been operated upon between 1933 and 1952 and 87 per cent were well after 5 years. It seems to me that our results are so much better since we combined radiation with surgery that I would be loath to change it until the evidence shows us something else. Of the 5 who died within 5 years, 2 showed no residual carcinoma in the uterus after operation. One of them alive after 5 years showed metastatic cancer of the ovary. Our radiation therapy consists of preoperative radium and supervoltage x-ray therapy, and with a repetition of the x-ray therapy postoperatively.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Dr. Wall is beginning his studied plan of treatment at a time when the earlier workers in this particular field, having learned that radiation therapy alone was a failure, can now discuss their results with preliminary radiation and subsequent surgery after a long period of observation. The survival figures have continued to be better since we began to realize that patients treated with radiation alone were wont to develop recurrence, as did some of those who received primary surgical treatment. Also, at that time, radium applications were not infrequently inadequate with respect to placement, type of radium sources, and dosimetry. With more recent and improved modality at his disposal, I hope that Dr. Wall will continue this plan of therapy with continued precision and enthusiasm, for which I commend him.

Having recently reviewed my personal series of 39 patients treated by this "planned therapy" method, and having observed them throughout the past 20 years, I note a 5 year plus survival rate of 92 per cent, including noncancer deaths. The combined rate of survival for those treated either by radium, x-ray, and/or surgery is 40 per cent.

DR. ARTHUR T. HERTIG, Boston, Mass.—I have three questions to ask the essayist: (1) Does he have any information as to what the prior biopsy of these 70 patients showed, if any were available? (2) What evidence, if any, does he have that abnormal activity of the endometrium in the form of polyps or hyperplasia played any role in the pathogenesis of this endometrial carcinoma? (3) What did the ovary look like in these 70 patients and were there any granulosa- or thecal-cell tumors?

DR. THOMAS C. PEIGHTAL, New York, N. Y.—This paper and its discussion emphasize the fact that some clinics do and some do not use preoperative radiation. We are in the midst of a surgical program, the end results of which must await further time. It is our belief that hysterectomy without preoperative radiation is practiced in many more centers than is generally realized. Upon verbal inquiry to the chiefs of 42 clinics throughout the country last fall, we ascertained that, at present, 20 do not use preoperative radiation in endometrial carcinoma. Since many of these programs are of fairly recent inception, it will be some time before we can compare their relative merits with those of the combined radiation plus surgery therapy which Dr. Wall has outlined for us.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—I am fully aware of the shortcomings of endometrial biopsy but I think we have a great deal to gain by using it frequently in the

office. With widespread recognition of the effectiveness of progesterone in the management of anovulatory dysfunctional bleeding, there is a temptation to treat preclimacteric patients without a preliminary curettage. Whenever we are tempted to do so, I believe we should at least take an endometrial biopsy. If we do so, we will occasionally pick up a completely unsuspected adenocarcinoma or a atypical hyperplasia. In our hands this procedure has repeatedly disclosed adenocarcinoma under extremely favorable circumstances, i.e., very early lesions.

I believe we should also consider this procedure whenever we contemplate sending a patient into the hospital for hysterectomy. Since 1949, we have been attempting to do this routinely on patients going in for hysterectomy, simply in an effort to avoid doing a hysterectomy for benign disease on a patient with unrecognized uterine malignancy. We all know that cytologic study picks up squamous-cell carcinoma when we have no suspicion of its presence. If we take smears routinely on all patients being referred into the hospital for probable hysterectomy we can thus eliminate the possibility of squamous-cell carcinoma, but such cytology alone will probably miss 30 per cent of adenocarcinomas. By routine office use of endometrial biopsy we will occasionally pick up an unsuspected adenocarcinoma. When we employ the other method of detecting unsuspected adenocarcinoma before hysterectomy, i.e., by curetting the uterus immediately preceding hysterectomy, we may sometimes fail to recognize early malignancy in the curettings, and few pathologists are willing to eliminate carcinoma by frozen sections of such curettings.

Taking endometrial biopsies routinely on women we are sending into the hospital, twice in 50 cases we have missed a malignancy in the fundus by preliminary biopsy in the office, but in 48 instances we have thus recognized adenocarcinoma before hospitalization. For this reason I feel that our chances of doing a hysterectomy in the presence of an unrecognized uterine malignancy will be minimized if endometrial biopsy is routinely employed before hysterectomy.

DR. CARL T. JAVERT, New York, N. Y.—I hesitate to make the tail of Dr. Wall's discussion kite any longer, but I think the crux of the problem lies in whether the disease is early and limited to the uterus or whether it has gone beyond it. That is also true of carcinomas of the breast, penis, tongue, or of any other organ. He has told us nothing about the effect of his radiation technique on the ovaries or pelvic lymph nodes. That gets me to my second point, and that is the staging of the disease. We stage carcinoma of the cervix and talk about prognosis in terms of Stage I or II, and we should do the same thing and have a similar yardstick to give prognosis for endometrial cancer. To base prognosis on whether radium was or was not placed in the uterus is not enough. It is important to know whether the disease has spread to the lymph nodes or not. That has always been a time-honored yardstick for prognosis. In about 100 patients with partial or fairly complete lymphadenectomy, we obtained positive nodes in 16 per cent. Only one of these has survived more than the 5 years, whereas, when the nodes are negative, a much higher survival rate is observed. When nodes are positive, we must think about endometrial carcinoma as having extended beyond the uterus and devise some other treatment to give these patients with carcinomatosis. The primary uterine lesion can be treated successfully by surgery alone or by radium and surgery. My preference is for primary surgery because of the increasing number of early lesions being discovered by cytologic smear.

DR. WALL (Closing).—Dr. Kimbrough asked about the reaction in the bladder and rectum to radium. We have not encountered any difficulty with these dosages but what we are trying to do is to evaluate one method of therapy over a long period of time. The 5 year salvage, of course, would not be of much value because of the small number of patients in the series and it would not be of statistical value. We anticipate that in years to come we can use this as a yardstick.

I want to apologize to Dr. McLennan. Apparently my paper did not make it clear that the 36 per cent of patients were my own cases from a former series. There were a good many who did not return for dilatation and curettage. Perhaps this is poor salesmanship on my part but it shows women will procrastinate. It was interesting to me to find out how many women would refuse to carry out recommended therapy.

We do fractional endometrial biopsies. If there is any question, the procedure can be repeated at the time of the first radium implantation. I want to emphasize that this represents a long-term program which I think someone should carry on. These are cases that have been handled by one individual and this may be of some value in years to come.

I think the therapy to the vaginal vault has not been well evaluated. Dr. Fletcher is hoping to report the value of radium in terms of the number of recurrences in the vault. I have not had any so far, but again this is a small series and they may all come at once.

Dr. Jones asked about endocrine imbalance. I cannot answer all of his questions. I think endocrine imbalance is one of the many vagaries in this study. We hope we will be able to do studies in retrospect as well as on new patients in regard to vaginal smears and endocrine assays.

Dr. Arneson has asked me questions for 2 days and nights—and he is smarter than I am. I think the only way I can answer his questions is to say that assessment of results is difficult because of the multiple variations. I was trying to emphasize these variations and I think we probably have shown to some extent that the two applications and the time-dose relationship may be of some value. This is another study about which we are trying to get more information. It does seem that the high dose delivered directly to the tumor over a short period of time has been more efficacious than reliance placed on external radiation because of the difficulty of limiting the dose to the tumor itself.

I think that also answers Dr. Sturgis' question concerning the reason for the 3 week interval. We think there is some sloughing of the tumor after the first application so that a second dose will be more effective.

Dr. Scheffey mentioned the improvement in dosage calculations. That is a distinct advantage and with these time-honored techniques, such as that of Heyman, and with better precision methods available, it may be possible to be more specific about the effects of this type of therapy.

Dr. Hertig asked about prior biopsies and we have no information on that point. He also asked about the incidence of polyps and hyperplasia. This is very pertinent to this problem and I hope somebody will come forth with more information. We did not have any patient with a feminizing tumor. The ovaries in our series did not prove to be of any value. We went back over our pathologist's reports but did not find significant changes reported in the stroma of the ovary. We believe that is because we did not pay enough attention to that possibility.

Dr. Peightal mentioned his surgical program, and I think that is the same thing we are trying to do in another field: evaluate another method of therapy. Over a long period of time it probably will be more beneficial to stick to one technique.

We have not had any significant complications. Aside from economic drawbacks I do not think we have had any complications.

Dr. Randall's comments on endometrial biopsy are most welcome. If more people would try a biopsy, even if it is one day before hysterectomy, the case might be more adequately evaluated. This has been a very useful tool in my experience.

Dr. Javert spoke of the limitation of the disease to the uterus and the difficulty in clinical staging, which is well known. There is no good staging of endometrial carcinoma and that makes it difficult to plan therapy. If we knew the extent of the tumor, it would be easier to know the ideal modalities of therapy. The ovaries were not studied before but after the uterus was removed; they did not show significant changes. The dosage of radium does not reach beyond 2 cm. This is a direct application of radium to the tumor itself and there is no possibility that it has any effect beyond that point. One of the most fundamental fields of development is the work of Javert's on lymph node involvement in endometrial carcinoma. Most of these people are very fat. We have carried out lymph node dissection where we can but so many times we cannot do it and this may be a weakness on our part.

AN EVALUATION OF INTRAFASCIAL HYSTERECTOMY*

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Historical Review

IT IS impossible to appreciate the present without viewing its relation to the past. The gynecologist of today, impressed with the simplicity of both abdominal and vaginal hysterectomy, may wonder why the details of their performance were not obvious a century ago. The painstakingly slow, but nonetheless remarkable, growth of the surgical art of gynecology is nowhere more evident than in the story of hysterectomy. When the operation is traced from its origin through the "tuneful turnings of time," evaluation of any of our present-day techniques falls into a proper setting. This becomes apparent if the historical thread is followed through the rich tapestry of the meetings of this Society,[1-97] an especially fitting source since hysterectomy and this Society originated about the same time. "The Transactions of this Society," said Charles C. Norris[76] in his presidential address of 1930, "constitute a complete record of the development of obstetrics and gynecology to the present time. Every obstetrical and gynecological procedure is described and discussed therein, the steps in the development of the art as well as the various theories advanced regarding the etiology and nonsurgical treatment of the diseases of women." Reviewing the foundations laid down by the efforts of the distinguished pioneers who raised pelvic surgery to an art, one is readily humbled. If such a reader of the record of the past, smug in his time-advanced point of vantage, occasionally gives way to a derisive smile, let him recall the admonition of Osler, "A man must be judged by his day, by his generation, and by his contemporaries."[98]

The Cervical Stump.—The first paper dealing with hysterectomy presented before this Society was the guest address of J. K. Thornton[1] of London in 1882 (Table I). During the next few years, the operation was discussed frequently, particularly from the viewpoint of technique.[5-10] The most serious problem of that day's hysterectomy was management of the cervical stump, liable to both death-dealing infection and fatal hemorrhage. In fact, it becomes clear to the most casual of readers that the operation of *total* hysterectomy must have been born because of fear of the cervix, not from choice. Termed then "a marvel of surgical audacity,"[6] subtotal hysterectomy was a

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formidable procedure. Surviving patients suffered untold misery during the recovery period. Their lamentable postoperative plight confined them to bed for 2 or 4 weeks "as miserable, unhappy wretched creatures numbed by laudanum."[11] Small wonder that E. E. Montgomery,[43] looking back in 1902, referred to the operation as "scientific butchery." The era of stump disasters came, happily, to an abrupt end. This major obstacle was overcome when separate ligation of each uterine artery became part of the operation, obviating the use of massive ligatures or crushing clamps on the cervix, thereby preventing delayed sloughing with its attendant hemorrhage. Farrar[79] credits this revolutionary technique to L. A. Stimson (1889) of New York. However, in the earlier Transactions, this progressive step—subtotal hysterectomy without massive ligature of the whole cervix—is attributed to Baer.[13] In 1919, J. R. Goffe[70] claimed priority when he told this Society in words bristling with indignation that the "Baer operation" should really be termed the "Goffe operation." Goffe's outburst was not out of joint with the times. Presentations before the American Gynecological Society during its formative years had a singularly personal quality, and proper assignment of priority was of great importance. In fact, the controversial discussions following the papers, frequently reflecting a high tone of rancor, were much more colorful than they are now.

TABLE I. HYSTERECTOMY AS PRESENTED TO THE AMERICAN GYNECOLOGICAL SOCIETY (1876-1955)

YEARS	NO. PAPERS	COMMENT
1876-84	3	First paper 1882
1885-94	18	Pedicle problems
1895-1904	26	Presidential address, guests, and debates
1905-14	14	Radical operation
1915-24	10	Ovaries appreciated
1925-34	8	Techniques refined
1935-44	11	Total vs. subtotal
1945-54	5	Radical operation revived
1955	1	Physiology

The Early Wertheim.—During the following decade, 1895-1904, hysterectomy was the topic of 26 papers before this Society (Table I). The interest it aroused may be appreciated by the fact that it was the subject of one presidential[44] and three guest addresses,[24, 29, 40] as well as of two planned debates.[19, 47] Shortly thereafter, the Transactions are replete with descriptions of the radical abdominal operation as applied to cancer of the uterus, there being six papers in Volume 37 alone.[55-60] It is interesting to note the relative similarity of results with the Wertheim operation, for each essayist seemed to have had about 50 per cent operability, 18 per cent primary mortality, and an approximate 50 per cent of 5 year cure.

Sparing Ovaries.—During the same period when hysterectomy for carcinoma seemed to be the most frequently discussed topic, the postoperative fate of the ovaries became a subject of wonderment.[53-54] This is of especial interest when one recalls the last of the series of 97 papers analyzed for this review,

that of Tenney, Parker, and Robbins,[97] which is devoted to experimental aspects of the same theme. From 1915 to 1924, opinions considerably at variance in regard to the desirability of sparing ovaries during hysterectomy appear in the Transactions.[62, 65, 67-68] In view of the present wide interest in the same troublesome decision, it is somewhat startling to find so many older papers with titles reminiscent of current articles. The words of E. H. Richardson,[68] written in 1918, could have been penned today: "The weight of evidence furnished by anatomical, experimental, and clinical investigations is overwhelmingly in favor of retention of sound ovaries both before and after the menopause age."

Vaginal and Total Techniques.—By 1925, hysterectomy, acquiring respectability, had attained its regular place in gynecologic therapy. Transactions of the succeeding decade are studded with refinements of technique.[73-75, 77-82] Evocative entreaties appear here for the first time inviting the more frequent use of vaginal hysterectomy for benign disease.[77, 80, 85] However, not all were enthusiastically received. Thus, Gellhorn,[77] sensing a rebuff for his recommendation that vaginal hysterectomy be performed under local anesthesia, wrote, "Neophobia is prevalent in all walks of life. I think that in less than 10 years from now what seems revolutionary today, will be a self-evident procedure."

Total abdominal hysterectomy burgeoned between 1935 and 1944. During this period appear many reports of cervical stump carcinoma,[86, 87, 92] as well as treatises dealing with anatomy of the total operation.[79, 81-83] Farrar,[86] in advocating the total procedure as the one of choice for benign conditions of the uterus, seemed to conclude the long debate with crystal-clear arguments.

TABLE II. EARLY AND RECENT RADICAL ABDOMINAL OPERATIONS FOR CARCINOMA OF CERVIX

SURGEON	YEAR	PRIMARY MORTALITY	UNCORRECTED 5-YR. SALVAGE
Clark	1912	18%	57%
Meigs	1951	0.8%	74.1% (all) 80.7% (I)

Today.—Transactions of the last decade offer an interesting contrast to those of a half-century earlier, particularly in the rebirth of radical hysterectomy for carcinoma of the cervix. Even though the surgical attack on carcinoma of the cervix by Meigs[95] may not be regarded as "a renaissance of the Wertheim operation," it is constructive to compare results. Decrease in primary mortality and improved salvage, resulting from careful selection of patients as surgical risks and advances of surgery, are readily apparent (Table II). In his presidential address delivered before this Society in 1903, entitled "The Surgical Treatment of Early Diagnosed Cancer of the Uterus, More Especially by Hysterectomy," J. E. Janvrin[44] anticipated words that were to be repeated 50 years later. In approving the use of hysterectomy for carcinoma of the cervix in the hands of expert operators, Janvrin said, "It is only by continuous work and the accumulation of the statistics in these major

operations at the hands of master operators that we can finally come to a definite understanding as to what we can accomplish and what we cannot accomplish in the surgical treatment of carcinoma of the uterus."

More recently, the Transactions reflect a liberalized attitude toward indications for hysterectomy. Well worth rereading are the discussions which followed the presentation of papers by Willson[93] on the use of hysterectomy in the climacteric woman and by Davis[94] on the controversial subject of cesarean hysterectomy.

This review of the past is not intended to disparage either the originality or the skill of an illustrious group of pioneers in pelvic surgery who laid strong foundations "upon which successive craftsmen have ingeniously fashioned the fine superstructures of present-day hysterectomy techniques."[82] The intent is rather to indicate the path along which hysterectomy has developed to the point where we are able to take certain of its indications for granted, to execute it simply, and to expect none but the best results. The operation has come a long way from its beginnings. If mortality alone were the criterion, real progress has been achieved (Table III). However, other desiderata are recognized. This point has been well put by Richardson[82] who said, "There is scant ground for self-congratulation on the part of any gynecologist upon the mere attainment of a low operative mortality. The acid test of results obtained is applied through insistence of unbiased follow-up observations continued not only during the period of hospitalization but also at intervals through later months, in order to determine the actual incidence of complications as well as the extent and duration of morbidity."

TABLE III. CHANGING PRIMARY MORTALITY OF HYSTERECTOMY (PERCENTAGE)

TYPE	DECADES			
	1876-1884	1895-1904	1925-1934	1935-1944
Vaginal	24	4.1	0.35	0
Subtotal	40	5	1.8	0.8
Total		9	1.3	0.6

Desiderata of Abdominal Hysterectomy

It cannot be denied that there is a recognizable trend to broaden the indications for vaginal hysterectomy. Since it is accompanied in properly selected patients by less morbidity, gives rise to fewer postoperative discomforts, and is somewhat less hazardous in trained hands than abdominal hysterectomy, such a trend is both salutary and understandable. Abdominal hysterectomy remains, however, the more frequently performed operation. A recent analysis[99] showed the ratio of abdominal to vaginal hysterectomy in our locality to be 75:25, a low usage of the vaginal operation in comparison with that of a vaginally dedicated gynecologist.[100] Although one may, in a given situation, discuss the relative merits and limitations of each route, there is no longer room to argue the choice between subtotal and total abdominal hysterectomy. The vast majority of total hysterectomies may be executed satisfactorily by

any one of several established methods. "But," as Richardson[101] wrote in 1929, "we are less interested today in the large percentage of successes that can be legitimately credited to the end-results of an operative procedure than we are in the smaller number of technical difficulties, complications, and failures that persistently crop up to mar our records."

The removal of the whole uterus for benign disease through an abdominal incision should have the following 5 objectives:

1. The planned dissection must be anatomic, permitting ease of execution and affording minimal loss of blood.

2. Bladder, ureters, and rectum must be consciously protected from injury, retaining maximum function postoperatively.

3. Hemostasis, particularly of the vaginal cuff and its angles, must be secure.

4. The vagina, none of which should be removed with the uterus, must remain well supported and free of granulations postoperatively.

5. Peritoneum must be preserved in such form as to insure complete coverage of the operative site, reducing the likelihood of intestinal adherence and possible obstruction.

Intrafascial Operation

The intrafascial technique of abdominal hysterectomy meets these requirements well. This operation has of late borne the eponymic of Aldridge[102] who, in describing his method of removing the uterus from within a complete circle of cervical fascia, emphasized that the procedure had evolved during a period of years from contributions of several gynecologists. As early as 1917, Worrall[103] had advised conservation of "a thin layer of musculature" of the cervix to prevent injury to the endopelvic fascia and to preserve "the arch of the vaginal vault." Later, Richardson[75] devised a technique of suturing the basal portion of the broad ligament and the stump of the uterosacral ligament to the vaginal angle on each side, affording "an efficient guarantee against later prolapse." He[101] recommended also isolation of cervical fascia anteriorly by a T-shaped incision before removing the uterus in order "to drop the ureters well away from the cervix." Mohler and Bishop,[104] Judd,[105] and Reich and Nechtow[106] described similar operations, preserving fascia anteriorly and emphasizing Richardson's dual rationale. The principle of incising and closing fascia separately from the vagina, *both* anteriorly and posteriorly, characterized the technique of Farrar.[79] The three-quarter intrafascial hysterectomy of Burch and Lavely[107] is similar but does not preserve the entire fascia anteriorly. The concept recently enunciated by Joseph[108] conserves a rim of fibroelastic cervical tissue as well as fascia, a procedure not unlike that recommended by Worrall.[103]

The present report comprises a review of 200 *private* patients subjected to intrafascial hysterectomy by the authors from January, 1949, through December, 1956. During this 8 year period, 180 ward or service patients also underwent such hysterectomy at the hands of senior residents, but they are not included in this analysis. We wish here to report only upon patients subjected to our personal follow-up. A preliminary comparison of the 2 groups,

private and ward, shows the anticipated difference in morbidity, a facet of gynecologic surgery emphasized by Weir[109] in his statistical report of 1,771 hysterectomies.

Technique

The surgical procedure described herein is the same in principle as that of Aldridge, differing only in several minor steps which will be noted. During the past 3 years, we have employed the low abdominal, transverse incision of Maylard because it affords better exposure of the pelvic cavity, eliminates the need for abdominal-wall retractors, and requires less packing away of intestines. The incisional technique is that recommended by Parsons and Ulfelder,[110] with the exception that we approximate skin edges by means of a continuous subcuticular suture of nylon which is withdrawn on the sixth postoperative day.

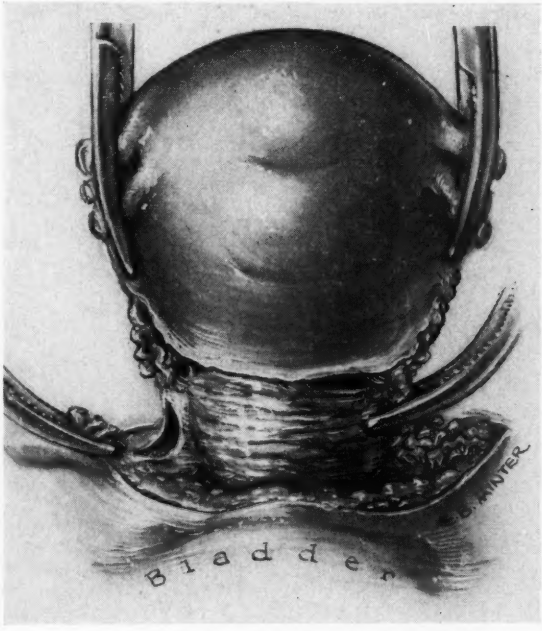


Fig. 1.

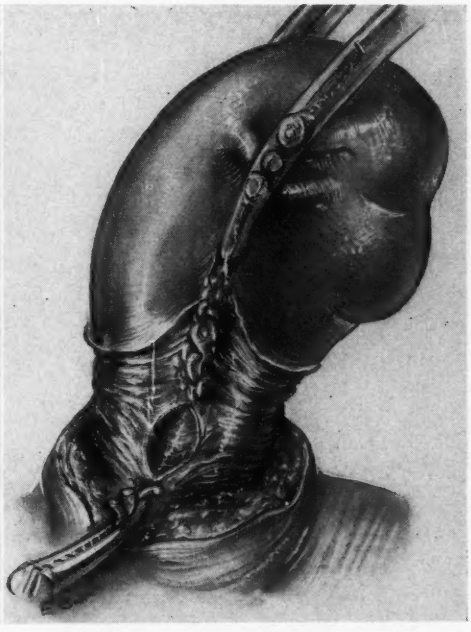


Fig. 2.

Fig. 1.—Creation of "oval window" in pericervical fascia when uterine vessels are clamped and severed.

Fig. 2.—Lateral view of "oval window" in fascia.

Mobilization.—The round ligaments are sutured and severed as usual. The uterovesical fold of peritoneum is incised transversely, creating an anterior peritoneal flap and allowing the bladder to be pushed downward after scissors' incision of the central attachment. The infundibulopelvic ligaments or ovarian ligaments and Fallopian tubes, depending on the need to remove adnexa, are ligated and severed. A bilateral flap of posterior peritoneum is prepared by incising it horizontally from the adnexal stumps to the uterosacral ligaments. The latter are then clamped at their uterine insertion, severed, and ligated. Small Metzenbaum scissors are employed to cut the peritoneum between the severed ligaments. This joins the right and left posterior peritoneal incisions and, after the free edge is pushed downward until the external cervical os is palpable through the vaginal wall, forms a straight posterior flap ideal for subsequent peritonization.

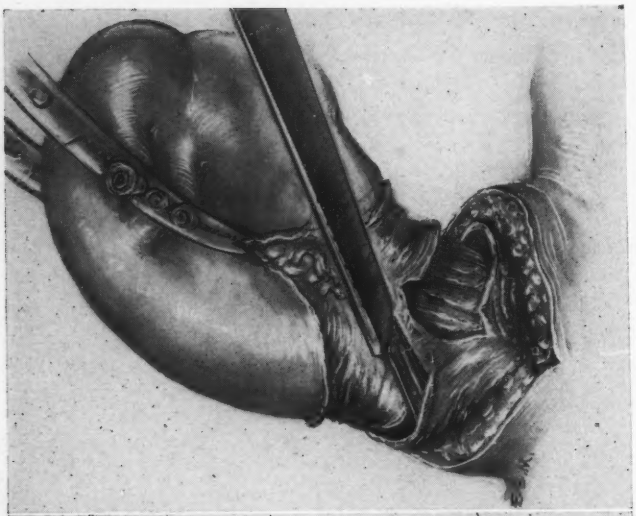


Fig. 3.

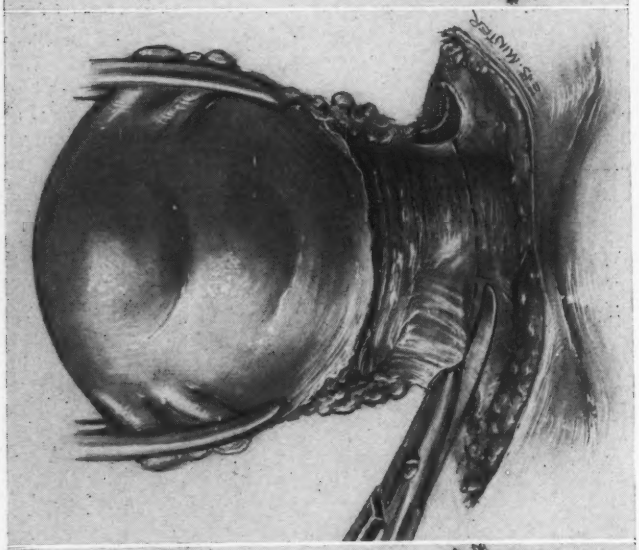


Fig. 4.

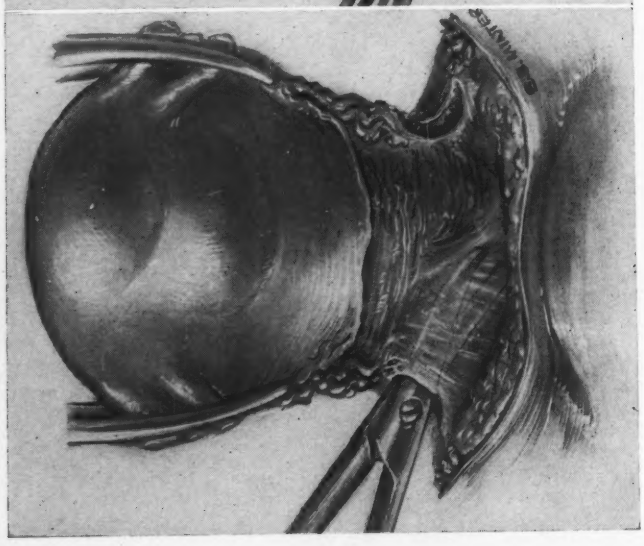


Fig. 5.

Fig. 3.—Dissection of anterior portion of pericervical fascia by scissors.
Fig. 4.—Transverse incision of fascia anteriorly.
Fig. 5.—Transverse incision of fascia posteriorly by scalpel.

Preparation of Fascia.—The uterine vessels of each side are cleared of surrounding adventitious tissue by means of sharp dissection, clamped at the level of the internal os, severed, and doubly ligated. This creates a lateral oval window in the fascia on each side (Figs. 1 and 2). Metzenbaum scissors now dissect the fascia from its bed and, engaging the free anterior edge of fascia on the surgeon's side, incise it transversely to the oval window of the opposite side (Figs. 3 and 4). The anterior fascial flap is then easily prepared by blunt dissection, allowing both bladder and ureters to fall further away. A similar fascial flap is created posteriorly but this usually requires sharp dissection (Fig. 5). The uterus may now be removed from inside the encircling but free fascial layer.

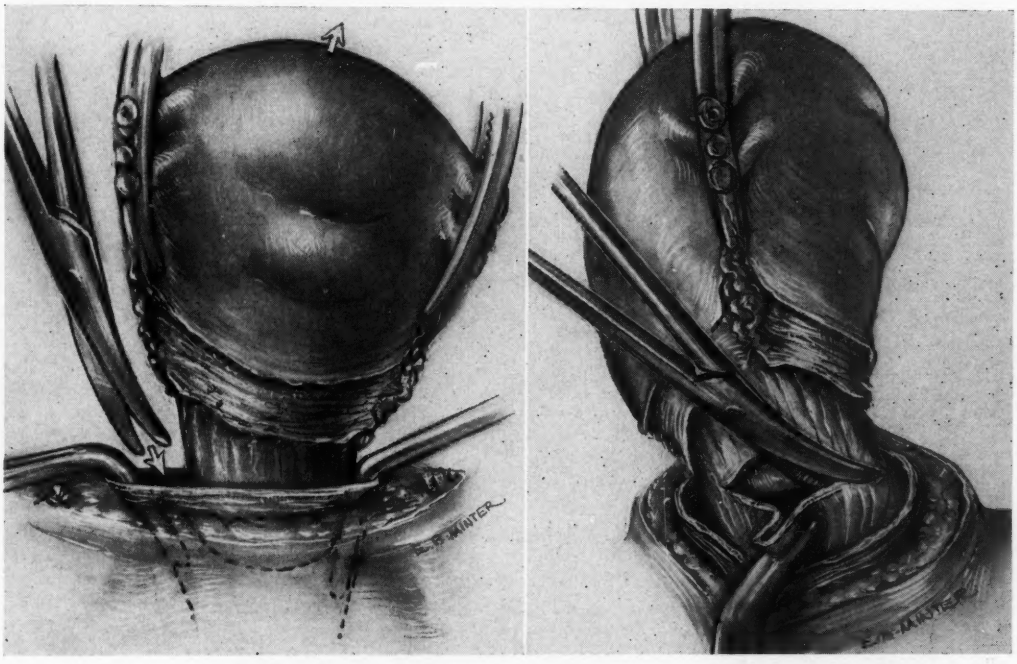


Fig. 6. Fig. 7.

Fig. 6.—Separation of cervix from parametrium with aid of Falk angle clamps.
Fig. 7.—Circumcision of vaginal vault, enabling last step of hysterectomy. Note Falk angle clamp holding parametrial tissue.

Excision.—A Falk angle clamp is placed parallel with and close to the cervix on each side *within* the fascial flaps, thus permitting severance of the parametrium and exposing the vagina laterally (Fig. 6). Strong upward traction upon the uterus, held now only by its attachment to the vagina, permits the surgeon to enter the vagina from his side by means of Mayo-type scissors. This affords excellent visibility, permitting circumcision of the vaginal vault without removing more than a scant tag of it (Fig. 7). Temporary vaginal traction sutures are employed to keep the operative site well in view, obviating the necessity of pulling upon the angle clamps.

Construction of Cuff.—Closure of the vagina begins successively at each angle with a suture contrived to evert (toward the operator) the edge and to incorporate the incised parametrial tissue held by the angle clamp (Fig. 8, *a*). This suture ligates the anastomotic area of the vaginal artery (from the hypogastric artery) and the azygos and cervical branches of the uterine artery. The remaining portion of the vaginal wound is closed with interrupted sutures,

everting the cut edges. This method of closure of the vagina has a dual advantage: It is hemostatic at the angles because it fixes the parametrial tissue firmly thereto and it prevents vaginal granulations because of the eversion principle. The fascia is now united with a continuous suture, the oval window of each side being closed by incorporating the free edge of the uterine vessel stumps (Fig. 8, *b*). It is envisaged that these steps, vaginal-edge eversion and separate closure of the fascia, encourage firm union of both structures, vagina and fascia, resulting in good support of the vaginal vault. Peritonization is accomplished by means of a continuous suture from left to right, burying the adnexal stumps. The suture material employed throughout is No. 0 chromic catgut.

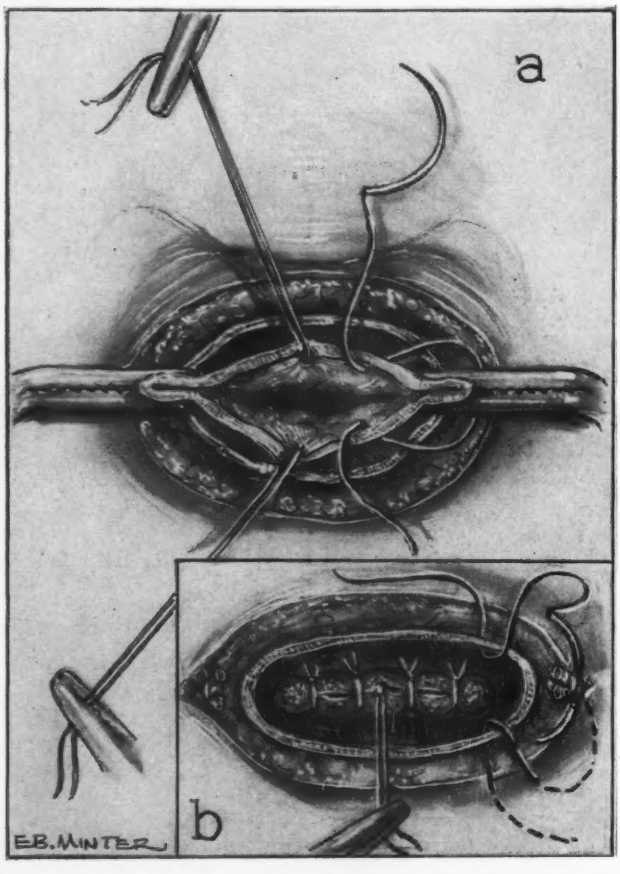


Fig. 8.—*a*, Everting angle suture embracing angle of vagina and parametrium. Note handy pair of traction sutures on vaginal wall.

b, Start of fascial closure, placing stump of uterine vessels into corner of fascia. Peritonization follows as separate layer.

Indications for Hysterectomy

The most frequent reason for total abdominal hysterectomy in this series, as in most others, was leiomyoma (Table IV). Although we prefer vaginal hysterectomy for removal of a myomatous uterus, frequently we are restrained from employing that route by observance of "certain relatively fixed contraindications."[111]

Secondary Conditions Found During Hysterectomy.—The primary indications for abdominal hysterectomy in this group are shown in Table IV. Secondary diagnoses, any pelvic condition discovered during operation but

not the principal reason for it, are listed in Table V. It is to be emphasized that carcinoma, regarded as a contraindication to the intrafascial technique, does not appear in either list. It is noteworthy also that endometriosis constituted the leading secondary condition encountered. Moreover, it should be mentioned that on 5 occasions, operations omitted from this analysis, we desisted from performing the planned total hysterectomy, being satisfied to accomplish a subtotal one because of widespread pelvic endometriosis.

TABLE IV. ABDOMINAL HYSTERECTOMY FOR BENIGN PELVIC DISEASE

INDICATION	NO.
Uterine.—	
Leiomyoma	162
Dysfunctional bleeding	7
Postpartum hemorrhage	1
Retroversion	1
Ovarian.—	
Endometriosis	16
Cystadenoma	6
Dermoid	2
Arrhenoblastoma	1
Tubal.—	
Hydrosalpinx	3
Tuberculosis	1
Total	200

TABLE V. ASSOCIATED PELVIC CONDITIONS FOUND DURING 200 ABDOMINAL HYSTERECTOMIES

FINDING	NO.
Endometriosis	19
Chronic salpingitis	4
Ovarian cystadenoma	3
Parovarian cyst	2
Granulosa-cell tumor	1
Total	29

Table V does not reflect the fact that we are addicted to prophylactic appendectomy, if the patient's condition permits, whenever we employ the abdominal route to pelvic surgery. The appendix had not been removed previously in 184 of the 200 patients in this series and, in all but 6, appendectomy was a concomitant procedure.

TABLE VI. ABDOMINAL HYSTERECTOMY IN 15 WOMEN UNDER 35

INDICATION	NO.
Leiomyoma of the uterus	7
Endometriosis	2
Dysfunctional bleeding	2
Postpartum hemorrhage	1
Retroversion of the uterus	1
Dermoid (sole ovary)	1
Hydrosalpinx (sole tube)	1
Total	15

Age of Patients.—The age of the patients in this series is expressed by decades in Fig. 9. Hysterectomy is not the treatment of choice in younger women with pelvic disease. On occasion, however, as pointed out by Jacobs and Daily,[112] it is better to remove the uterus of a younger woman, especially

if she has had the children she desired, rather than to subject her to an "incomplete and 'tinkering' surgical procedure." Typical of this thesis is the story of one of the 15 patients of our series who were less than 35 (Table VI). She was 30 years of age, had had 3 children, and was subjected to hysterectomy because of symptomatic uterine retroversion which had been relieved repeatedly by manual reposition followed by use of a pessary.

Results

No death occurred among the patients in this series.

Morbidity.—As emphasized by Watts and Kimbrough,[99] there is presently no adequate standard upon which to base postoperative morbidity unless one employs the rigid criteria applied to obstetrics, a practice which exaggerates the morbidity of pelvic surgery. In analyzing this series, we defined morbidity as a temperature of 100.4° F. or more on any 2 successive days after the first postoperative day. By this standard, only 20 of the 200 patients (10 per cent) were morbid.

During the past 4 years (1953-1956), we have employed 2 penicillin-streptomycin vaginal suppositories, one inserted the night prior to operation and the other at the conclusion of hysterectomy. The number of patients is too small to be analyzed statistically but our data support the contention of Schnall[113] and others[114-115] that the use of 2 such suppositories reduces morbidity. It is important to note, however, that we do *not* employ prophylactic systemic chemotherapeutic or antibiotic agents. Subscribing to the dicta so well enunciated by McKittrick,[116] we use them only when specificially indicated.

Complications

Intraoperative.—It is difficult to analyze minor complications which take place during an operation. From the dictated notes describing each operation of this series, however, we have learned that no major complication such as bowel, bladder, or ureteral injuries occurred. On 3 occasions, total hysterectomy was accomplished by bisecting the cervix and removing the anterior and posterior lips separately. Troublesome hemorrhage during operation took place in 2 patients, neither one to the degree of shock. In one of the 2, the bleeding resulted from improper ligation of the left ovarian vessels and their subsequent retraction from view; and in the other, continuous oozing from the subfascial bed required several figure-of-eight sutures.

TABLE VII. POSTOPERATIVE COMPLICATIONS OF 200 ABDOMINAL HYSTERECTOMIES

COMPLICATIONS	NO.	
Minor.—		
Vault granulations	26	
Cuff bleeding	4	
Wound hematoma	2	
Wound infection	2	
	—	
		34
Major.—		
Thrombophlebitis	2	
Paralytic ileus	2	
Atelectasis	1	
Retroperitoneal hematoma	1	
Dehiscence and eventration	1	
	—	
		7
Total		41

Postoperative.—Minor complications, those common to most abdominopelvic operations, were relatively infrequent (Table VII). Granulation tissue of the vaginal vault, sought for and electrically cauterized at the initial follow-up visit (6 weeks after operation), was found in only 26 patients (13 per cent). This low incidence—even lower than that following vaginal hysterectomy[111]—is probably attributable to the eversion principle employed in construction of the cuff. The 4 instances of bleeding from the cuff occurred within the immediate postoperative period and were each controlled by vaginal packing alone. No patient experienced delayed bleeding from the vaginal cuff.

The case of severe retroperitoneal hemorrhage eventuating in shock and requiring reoperation emphasized the need for care when peritonization is performed. The left ovarian artery had been unwittingly pricked by the needle employed in the purse-string suture and inversion of that stump, resulting in massive retroperitoneal hematoma. During reoperation, treatment included evacuation of clots and packing of the retroperitoneal space; shock was, of course, combated by transfusion of blood.

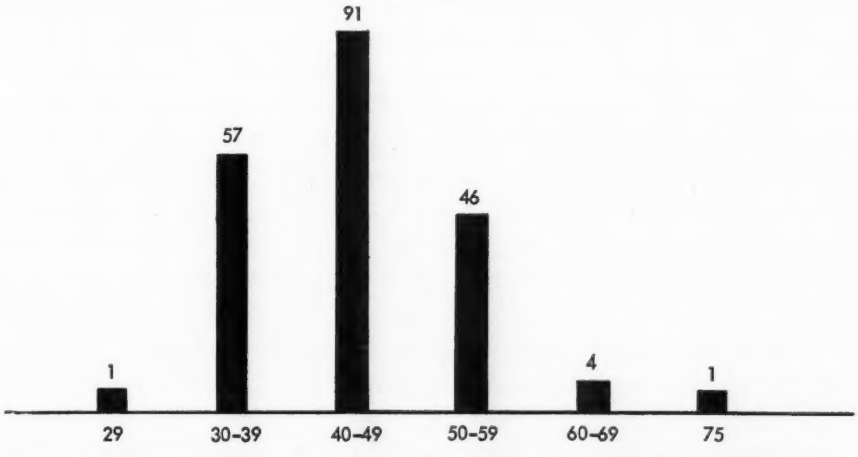


Fig. 9.—Age groups of 200 patients subjected to intrafascial hysterectomy.

The single wound dehiscence and eventration, successfully treated by through-and-through suturing with wire, took place before our use of the Maylard incision. On the other hand, the sole incisional hernia occurred in a patient in whom the low transverse incision had been employed. It may be significant that the herniation occurred in a wound in which we had not employed the musculofascial mattress-type suture advocated by Parsons and Ulfelder.[110] It was repaired successfully one year postoperatively.

We have no figures with which to support our impression that this group of patients suffered no overt psychologic reactions to total abdominal hysterectomy. It is appreciated that such counteractions have no direct relation to the precise data, such as age, parity, symptoms, and morbidity, usually assayed in a retrospective surgical analysis. They bear rather a more direct connection to such intangible factors as the patient's acceptance of the loss of both menses and reproductive function and her understanding of the meaning of "hysterectomy." Unless the latter is clearly defined for her, she will have an incomplete, often bizarre, mental picture of the fruits of such an operation. Fox and associates[117] have shown that patients who are poorly prepared psychologically for operation tend to have higher morbidity. Sturgis and his group[118] are attempting to assess this deficit on our part by analysis of the

patient's reaction immediately postoperatively. It should be apparent to all who practice gynecology that the time devoted *preoperatively* to careful discursive explanation is time well spent.

Summary and Conclusions

As an introductory background to this retrospective analysis of 200 patients subjected to the intrafascial type of abdominal hysterectomy, 97 presentations before the American Gynecological Society on the general subject of hysterectomy have been briefly reviewed. This historical collection, illustrating the continuum which underlies and connects the development of the surgical art of gynecology, bespeaks the personal dexterity of our professional forebears. The 97 papers also dramatize the fact that these gifted pioneers, striving to develop surgical techniques, worked in a milieu charged with attainment and great promise. The collective memoir also portrays the quasi-competitive aspects of vaginal or abdominal and total or subtotal hysterectomy. Although one may, in a given situation, discuss the relative merit of the vaginal and the abdominal approaches, there is no longer room to debate the choice between subtotal and total abdominal hysterectomy. Any modern technique for the latter must offer certain anatomic and physiologic desiderata. The intrafascial procedure (Aldridge) does.

The several advantages of the intrafascial technique of abdominal hysterectomy include preservation of the supporting tissue of the vaginal vault, protection of the bladder and ureters from the trauma of dissection, and prevention of excessive granulation tissue of the vagina during the healing phase.

Preservation of the pericervical fascia separately from the vagina clearly permits total hysterectomy with minimal disturbance of the urinary system. It also allows careful approximation of the fascia during closure. During this process the cardinal ligaments of each side, as well as the uterosacral ligaments, are sutured to the fascial envelope as it is closed. Closure of the vagina is accomplished with the aim of everting (toward the operator) its mucosa so that no healing edges remain in the vaginal space but are made rather to lie against the united fascial layer. The latter, really the transverse cervical ligament, is a strong sheath of tissue to which the everted vaginal edges adhere during healing, thereby elevating the vault.

The smallness of the series of 200 private patients does not allow statistical treatment of the data, a shortcoming offset, perhaps, by long-term postoperative observations.

References

Historical Aspects

Trans. Am. Gynec. Soc.: 1. Thornton, J. K.: 7: 158, 1882. 2. Jackson, A. R.: 8: 172, 1883. 3. Munde, P. F.: 9: 195, 1884. 4. Sutton, R. S.: 11: 419, 1886. 5. Bantock, G. G.: 12: 201, 1887. 6. Dudley, E. C.: 13: 191, 1888. 7. Byford, H. T.: 14: 413, 1889. 8. Byford, H. T.: 15: 127, 1890. 9. Etheridge, J. H.: 15: 352, 1890. 10. Byford, H. T.: 16: 212, 1891. 11. Boldt, H. J.: 17: 177, 1892. 12. Polk, W. M.: 17: 215, 1892. 13. Baer, B. F.: 17: 235, 1892. 14. McMonagle, B.: 17: 376, 1892. 15. Baer, B. F.: 18: 62, 1893. 16. Goffe, J. R.: 18: 79, 1893. 17. Sutton, R. S.: 18: 330, 1893. 18. McLaren, A.: 18: 451, 1893. 19. A debate: 19: 16, 1894. 20. Montgomery, E. E.: 19: 301, 1894. 21. Henrotin, F.: 19: 308, 1894. 22. Gordon, S. C.: 20: 30, 1895. 23. Emmet, T. A.: 20: 38, 1895. 24.

Jacobs, C.: 20: 194, 1895. 25. Wathen, W. H.: 20: 208, 1895. 26. Sutton, R. S.: 20: 241, 1895. 27. Ashton, W. E.: 20: 515, 1895. 28. Gordon, S. C.: 21: 104, 1896. 29. Segond, P.: 21: 133, 1896. 30. Byrne, J.: 21: 147, 1896. 31. Byford, H. T.: 21: 365, 1896. 32. Noble, C. P.: 22: 38, 1897. 33. Boldt, H. J.: 23: 99, 1898. 34. Cushing, E. W.: 23: 209, 1898. 35. Noble, C. P.: 24: 19, 1899. 36. Vineberg, H. N.: 24: 134, 1899. 37. Wathen, W. H.: 24: 369, 1899. 38. Kelly, H. A.: 25: 207, 1900. 39. Davenport, F. H.: 25: 222, 1900. 40. Richelot, C. G.: 25: 280, 1900. 41. Kirkley, C. A.: 26: 116, 1901. 42. Edebohls, G. M.: 26: 150, 1901. 43. Montgomery, E. E.: 27: 163, 1902. 44. Janvrin, J. E.: 28: 3, 1903. 45. Johnson, J. T.: 28: 43, 1903. 46. Noble, G. H.: 28: 58, 1903. 47. A debate: 28: 172, 1903. 48. Frederick, C. C.: 30: 137, 1905. 49. Gellhorn, G.: 30: 141, 1905. 50. Currier, A. F.: 31: 143, 1906. 51. Stone, I. S.: 35: 391, 1910. 52. Ward, G. G., Jr.: 35: 429, 1910. 53. Dickinson, R. L.: 36: 324, 1911. 54. Polak, J. O.: 36: 329, 1911. 55. Clark, J. G.: 37: 269, 1912. 56. Peterson, R.: 37: 295, 1912. 57. Taylor, H. C.: 37: 309, 1912. 58. Taussig, F. J.: 37: 322, 1912. 59. Cullen, T. S.: 37: 329, 1912. 60. Neel, J. C.: 37: 345, 1912. 61. Stone, I. S.: 39: 385, 1914. 62. Vineberg, H. N.: 40: 59, 1915. 63. Peterson, R.: 41: 518, 1916. 64. Child, C. G.: 41: 585, 1916. 65. Graves, W. P.: 42: 208, 1917. 66. Bissell, D.: 42: 609, 1917. 67. Polak, J. O.: 43: 105, 1918. 68. Richardson, E. H.: 43: 114, 1918. 69. Bissell, D.: 43: 157, 1918. 70. Goffe, J. R.: 44: 22, 1919. 71. Vineberg, H. N.: 46: 81, 1921. 72. Cashman, B. Z.: 51: 196, 1926. 73. Spalding, A. B.: 51: 214, 1926. 74. Masson, J. C.: 52: 252, 1927. 75. Richardson, E. H.: 53: 148, 1928. 76. Norris, C. C.: 55: 1, 1930. 77. Gellhorn, G.: 55: 218, 1930. 78. Goff, B. H.: 58: 237, 1933. 79. Farrar, L. K. P.: 59: 291, 1934. 80. Heaney, N. S.: 59: 307, 1934. 81. Goodall, J. R.: 61: 144, 1936. 82. Richardson, E. H.: 61: 157, 1936. 83. Farrar, L. K. P.: 62: 11, 1937. 84. Richardson, E. H.: 62: 145, 1937. 85. Danforth, W. C.: 63: 212, 1938. 86. Farrar, L. K. P.: 64: 248, 1939. 87. Behney, C. A.: 65: 26, 1940. 88. Miller, H. E., and Prejean, O.: 66: 79, 1941. 89. Danforth, W. C.: 66: 86, 1941. 90. Holden, F. C.: 67: 27, 1942. 91. Waters, E. G.: 67: 134, 1942. 92. Carter, B., Thomas, W. L., and Parker, R. T.: 71: 229, 1948. 93. Willson, J. R.: 73: 146, 1950. 94. Davis, M. E.: 74: 148, 1951. 95. Meigs, J. V.: 74: 164, 1951. 96. Phaneuf, L. E.: 75: 27, 1952. 97. Tenney, B., Parker, F., Jr., and Robbins, S. L.: 78: 189, 1955.

Present Report

98. Cushing, H.: Life of Sir William Osler, New York, 1940, Oxford University Press, p. 711.
99. Watts, W. F., and Kimbrough, R. A., Jr.: Obst. & Gynec. 7: 483, 1956.
100. Allen, E., and Peterson, L. F.: Obst. & Gynec. 3: 240, 1954.
101. Richardson, E. H.: Surg., Gynec. & Obst. 48: 248, 1929.
102. Aldridge, A. H., and Meredith, R. S.: AM. J. OBST. & GYNEC. 59: 748, 1950.
103. Worrall, R.: Am. J. Obst. 76: 894, 1917; M. J. Australia 7: 429, 1920.
104. Mohler, R. W., and Bishop, E. H.: AM. J. OBST. & GYNEC. 50: 489, 1945.
105. Judd, G. E.: West. J. Surg. 55: 2090, 1947.
106. Reich, W. J., and Nechtow, M. J.: Am. J. Surg. 35: 670, 1948.
107. Burch, J. C., and Lavely, H. T.: Ann. Surg. 136: 720, 1952.
108. Joseph, M.: Am. J. Surg. 89: 608, 1955.
109. Weir, W. C.: AM. J. OBST. & GYNEC. 56: 1151, 1948.
110. Parsons, L., and Ulfelder, H.: Atlas of Pelvic Operations, Philadelphia, 1953, W. B. Saunders Company.
111. Israel, S. L.: AM. J. OBST. & GYNEC. 69: 87, 1955.
112. Jacobs, W. M., and Daily, H. I.: Surg., Gynec. & Obst. 102: 539, 1956.
113. Schnall, N.: AM. J. OBST. & GYNEC. 65: 73, 1953.
114. Fletcher, P. F.: South. M. J. 43: 715, 1950.
115. Turner, S. J.: AM. J. OBST. & GYNEC. 60: 806, 1950.
116. McKittrick, L. S., and Wheelock, F. G.: Surg., Gynec. & Obst. 99: 376, 1954.
117. Fox, H., Rizzo, N., and Gifford, S.: Psychosom. Med. 16: 186, 1954.
118. Sturgis, S. H., Robey, H., Pierson, H., Gates, P., Plaut, T., and Menzer-Benaron, D.: Obst. & Gynec. 7: 363, 1956.

Discussion

DR. ALBERT H. ALDRIDGE, New York, N. Y.—This report includes a summary of many scientific contributions which, during the past 65 years, have led to the development of modern techniques for complete abdominal hysterectomy. We can hardly fail to agree that the success and safety of present-day techniques can be attributed to the fact that they are based on sound anatomic and physiologic principles.

An analysis of the outcome of 200 complete abdominal hysterectomies has been presented. It shows no mortality, a low incidence of morbidity and surgical complications, and no injuries to the urinary tract. The end results support the contention of the authors that the technique which they used and refer to as the infrafascial operation is a relatively simple, safe procedure.

Whenever the safety and success of any surgical procedure is established, there is always a tendency to broaden its indications for treatment of some conditions which can be and should be treated by more conservative methods. It seems certain that this Society should not approve the indications for one hysterectomy specifically referred to in the text of the report which has been presented. A woman 30 years of age had three children and wished no more. Her troublesome pelvic symptoms from a retroverted, presumably normal uterus had been repeatedly relieved by replacement of the uterus and insertion of a retroversion pessary. It was obviously decided to settle both of this young woman's problems by hysterectomy.

There are few justifiable indications for removal of a normal uterus at 30 years of age. They should not include hysterectomy to prevent future pregnancies or to relieve pelvic symptoms from a retroverted uterus. Treatment of such conditions by more conservative procedures is sure to protect some women against development of the disturbing emotional and physical symptoms of an early and prolonged artificial menopause.

The excellent end results shown in this report were produced by two skillful, experienced gynecologists from a painstaking follow-up of 200 private patients who had had complete abdominal hysterectomies by a carefully standardized surgical technique. To this extent their end results are important and commendable.

During the past 15 years a high percentage of complete abdominal hysterectomies at the Woman's Hospital has been done by a technique which is in principle the same as that which has just been described. End results after two series totaling 1,500 hysterectomies have been carefully analyzed. In the first series of 500 there were 2 postoperative deaths from vascular accidents. One was due to a cerebral thrombosis in a patient who had syphilis and advanced arteriosclerosis. The second death was probably due to a pulmonary embolus. It occurred suddenly on the ninth postoperative day of what had appeared to be a normal convalescence. The patient was 50 years of age and had been under observation for rheumatic heart disease for over 30 years. In the second series of 1,000 hysterectomies there were no deaths. In none of the 1,500 hysterectomies were there any injuries to the ureters or bladder, or any postoperative urinary tract fistulas. In other respects our end results as regards the incidence of postoperative morbidity and complications compare favorably with those just reported.

Our 1,500 hysterectomies were done on approximately equal numbers of ward and private patients. They were done by a large number of attending and resident surgeons. About 85 per cent of the hysterectomies on ward patients were done by residents alone or under supervision. There is probably no better test of the safety and success of any surgical technique than the results which it produces in the hands of a large group of surgeons who have varying degrees of ability, training, and experience.

About 40 years ago, Worrall called attention to the cuff of connective tissue or fascia which surrounds the cervix and vagina. It has proved to be one of the most important contributions to the development of a simple, safe technique for complete abdominal hysterectomy. By working within this cuff, the proximal ends of the cardinal ligaments can be easily detached from the uterus and the cervix can be released from the vaginal vault without any risk of injury to the ureters, bladder, or bowel. Blood loss from this procedure should be minimal. Wound healing of structures in and about the vaginal vault is promoted by a minimum of damage to their blood supply. Fixation of the cardinal ligaments to the fornices of the vagina leaves a well-supported elastic vault.

There are certain steps in technique by which surgical accidents and the complications of complete abdominal hysterectomy can be prevented. Dissections should be carried out in natural planes of cleavage. The pelvic structures should be kept under tension while dissections are being made. This can be accomplished by moderate upward traction on the uterus. All pedicles should be ample and securely ligated. Many ureteral

injuries and ligations have occurred during attempts to control bleeding from retracted blood vessels in the broad and infundibulopelvic ligaments. Such difficulties occur as a rule when ligatures on pedicles are inadequate or become dislodged.

By present-day techniques, complete abdominal hysterectomy has become a relatively simple, safe surgical procedure. On the other hand, gynecologists and urologists are still being called upon to treat postoperative ureteral ligations and urinary tract fistulas. For this reason reports such as the one just presented seem important by calling attention again to available techniques by which the risks and complications of complete abdominal hysterectomy can be prevented.

DR. RICHARD W. TE LINDE, Baltimore, Md.—Not only the practical side of this paper but the historical side has been very entertaining to me since I am old enough to have heard many of the papers mentioned. I believe the first meeting I attended was right here when Dr. Gellhorn gave his paper and he was really taken over the coals. We have now become more polite and soft spoken. In closing he said, "I take it my presentation was not received very well but I still believe in it." And he did.

I would like to go so far as to say that any hysterectomy other than an intrafascial for benign disease is an antequated operation. I do not mean that you can apply this technique every time but when there is no contraindication it is certainly a superior technique. In the early 30's, Dr. Richardson taught us an intrafascial hysterectomy which in principle is the same as this. There is little choice between it and Dr. Aldridge's technique. I like to use the knife anteriorly, although I noticed that Dr. Israel uses the scissors, but that is a personal preference and not important.

As I see it, there are three distinct advantages to intrafascial abdominal hysterectomy: (1) It avoids damage to the urinary tract; I have seen no damage to bladder or ureter. (2) About once in perhaps 200 hysterectomies, some 10 to 12 days after operation there is vaginal hemorrhage, and I mean a very sudden and severe hemorrhage. I can recall no bleeding like that in our cases since we have used the intrafascial technique because you have stopped the blood supply by separating the fascia from the upper vagina and ligating the necessary blood vessels so the uppermost vagina does not have the blood supply that it does if the fascia is left attached. (3) The suspension of the vaginal vault is good. I had this last point brought home to me when an ex-resident wrote back to me that he had seen more prolapses of the vagina following hysterectomy in the 6 months he had been in his town than in the 5 years of service in our hospital. The utilization of the fascia and base of the broad ligament in support of the vagina is an important factor in preventing prolapse of the vagina.

I wish to support Dr. Israel in his hysterectomy in the 30-year-old woman. I believe there is a place for this procedure in a woman in her early 30's with a normal uterus. For example, a woman who has three children, retroversion, and first-degree descensus and is made miserable by her symptoms; she has all the children she wants. Psychologically and physically I think you would do her a favor by performing a hysterectomy. The only way I would differ with Dr. Israel is that I would do the hysterectomy vaginally and correct the accompanying cystocele and rectocele that usually occur in such a case.

DR. ISRAEL (Closing).—The story of the 30-year-old patient was detailed in the body of the paper to indicate that we think there *is* a place for hysterectomy in the younger woman.

Dr. Te Linde's remarks about Dr. Gellhorn's paper were delightful.

The contraindications for this operation were mentioned by Dr. Te Linde and I would agree. In the paper itself are detailed five instances in which the operation could not be accomplished because subtotal hysterectomy had to be done.

The four instances of postoperative hemorrhage from the vagina occurred within the first 24 hours; they were mild and were controlled by packing alone.

CINEFLUOROGRAPHIC STUDIES OF THE BLADDER AND URETHRA IN WOMEN

I. Urethrovesical Relationships in Voluntary and Involuntary Urination*†

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(From the Departments of Obstetrics and Gynecology, Radiology, and Surgery (Division of Urology) of the University of Rochester School of Medicine and Dentistry)

MUCH has been written about the structure and function of the bladder and urethra in normal and abnormal conditions. A staggering volume of accumulated literature was ably compiled and reviewed by Ullery[1] in 1953. Investigators such as Hodgkinson[2] in this country, Ardran[3, 4] and Jeffcoate and Roberts[5, 6] in England, and many others continue to make important contributions. In spite of this excellent body of knowledge there are still some significant differences of opinion upon such fundamental matters as, for example, the nature and function of the internal and external sphincters.

Micturition consists of a series of rapid voluntary, involuntary, and reflex movements. Complex muscular activity such as this does not yield readily to analysis. Static methods of study leave much to be desired. This is one of the reasons we know so little about micturition. By use of the fluoroscope Muellner[7, 8] studied the motion of normal micturition. In 1954, Benjamin and co-workers[9] of this university and Hinman[10] of California independently presented some of the earliest clinical cinefluorographic studies of urination. Ardran[3, 4] has utilized rapid serial radiography to study the bladder and urethra in women. His method has permitted from 40 to 100 individual exposures at a rate of two, three, or four frames per second from the lateral view.

The purpose of this paper is to present the adaptation of cinefluorography to the study of micturition in women. Some preliminary observations of the urethra and the base of the bladder during voluntary and involuntary urination will be presented.

Materials and Method

All women chosen for this study were infertile so any potential genetic hazards of radiation were eliminated. Normal urination was studied in nulliparous and multiparous patients in the childbearing age who had diseases such as intraepithelial carcinoma or tubal occlusion. Abnormal micturition was studied in women with stress incontinence, cystocele, or combinations of the two.

*This investigation was supported in part by the James Picker Foundation on recommendation of the Committee on Radiology, National Academy of Sciences-National Research Council, and the Adelina Ritter Shumway Research Fund.

†Presented at the Eightieth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 27-29, 1957.

Before studies were made the clinical history was taken and the patient was specifically questioned about stress incontinence, urgency, etc. A complete examination including pelvic evaluation was recorded.

After the patients were prepared, an 18 Fr. soft rubber catheter was inserted into the bladder under sterile precautions. The bladder was then distended by gravity flow with 150 to 200 ml. of 50 per cent Miokon* contained in a 20 ml. glass cylinder held 15 cm. above the symphysis pubis. The temperature of the solution was 80° F. When the patient had the first slight urge to urinate the flow was stopped and the motion picture study was started.

Cinefluorographic examination of the bladder began with the visualization of the opaque filled bladder in the anterior-posterior and oblique projections with the catheter in place. The origin of the urethra from the bladder base was thus observed. The degree of obliquity of the patient was chosen so that the entire course of the urethra was accurately recorded. Following the removal of the catheter, the patient was then asked to strain and to cough. The results of these actions on urination were recorded in the anterior-posterior and oblique projections. The patient then voluntarily initiated micturition, and while this action was filmed in the oblique projection, several voluntary starts and stops of the urinary stream, terminal emptying of the bladder, and the type and amount of residual were recorded.

The equipment currently in use consists of a G.E. Imperial Tilt Table, KX-19 transformer and control panel. The "cine" equipment is a Phillips image intensification tube and a 35 mm. Arriflex camera; a periscope provides viewing for the operator. The studies may be recorded at speeds of 7.5, 15, or 30 frames per second. Exposures are made simultaneously with fluoroscopic visualization of the action by the operator. Kodak Special Linagraph Ortho 35 mm. film (0-1130) is used, processed in Kodak D-16 Developer for 6 minutes and then is optically printed on 16 mm. film for projection and study purposes. The 35 mm. negatives are stored and are never projected but may be used to make additional prints if required.

Factors for an average patient are 10 Ma., 130 KVP., and for a 2 minute routine study a skin dose rate at the table surface including backscatter with the system described is about one r per second for the 4½ inch circle involved.

The exposures may be analyzed in three ways:

1. Projection at slow and average speed (10-20 frames per second. Frame refers to a single exposure). From such views the broad features of motion are observed.

2. Projections at extra slow speed (2-3 frames per second or by single frame) to observe finer degrees of change.

3. Drawing or reproduction of individual frames for detailed observation and measurement of changes.

Forty-two women have been studied during the past two years. Between 500 and 2,000 individual frames have been processed and studied for each patient. Much of our earlier study was directed toward improvement of equipment and technique. At present some of our difficulties concern the relatively small field (4½ inches) and the heat load and electrical limitations.

Results

Two distinct and different types of urination have been observed, voluntary and involuntary. Each is produced by different voluntary and involuntary muscular activities and in many patients both types of activity may be seen.

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*Generous supplies of Miokon were supplied by the Mallinckrodt Chemical Works, St. Louis, Mo.

Voluntary Urination.—Voluntary urination which is free and uninhibited occurs with little straining. Not every woman can accomplish this act upon command in the presence of cameras, x-ray equipment, and the required personnel. Examination of the motion picture will show whether or not the patient has strained in her effort to initiate micturition.

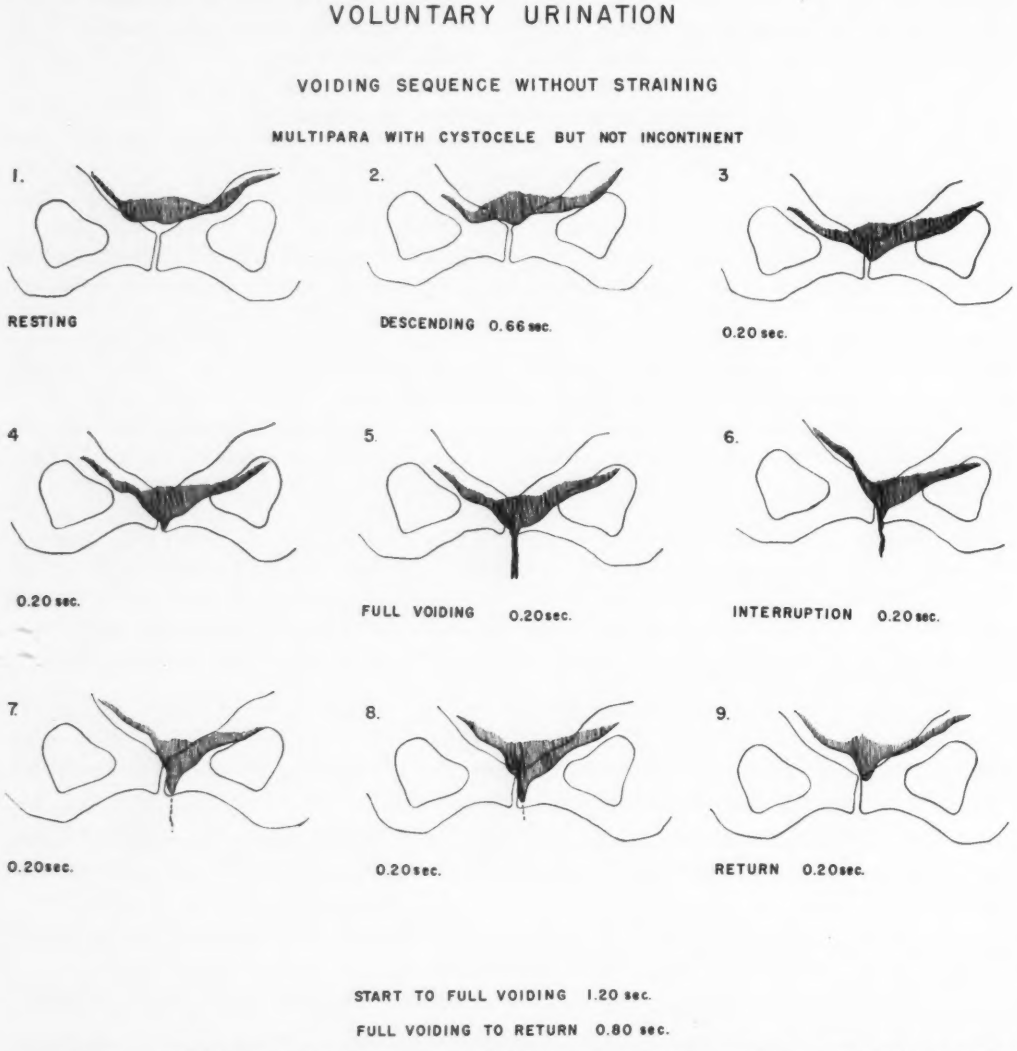


Fig. 1.—Anterior-posterior views. No. 324943, aged 32 years, para x. Frames 1-4 show descent of broad base (cystocele) with development of some funneling and a small infundibulum ("beak") in No. 4. The short time interval from the start to full voiding suggests lack of straining. Interruption begins with simultaneous elevation of bladder base and constriction of mid-urethra, frame 7. (An unusual finding is the excessive elevation of the right bladder base.) Constriction of mid-urethra stops flow of urine. The contents of the proximal urethra are returned to the infundibulum (frame 8) and the infundibulum slowly constricts.

Commencement of urination: The shape of the bladder varies with the quantity of fluid in it. With moderate (150 ml.) filling, the base of the bladder is usually flat or slightly angulated (Figs. 1, 2, 5). As the voluntary musculature of the urogenital diaphragm relaxes, the posterior base of the bladder and the urethrovesical junction descend while there is downward motion of the anterior bladder wall (Fig. 5). Thus a rocking motion is produced. The amount

of descent varies and depends in part upon the increased intra-abdominal pressure and the natural supports of the bladder. A small infundibulum or "beak"[3] may precede urination (Figs. 1, 5).

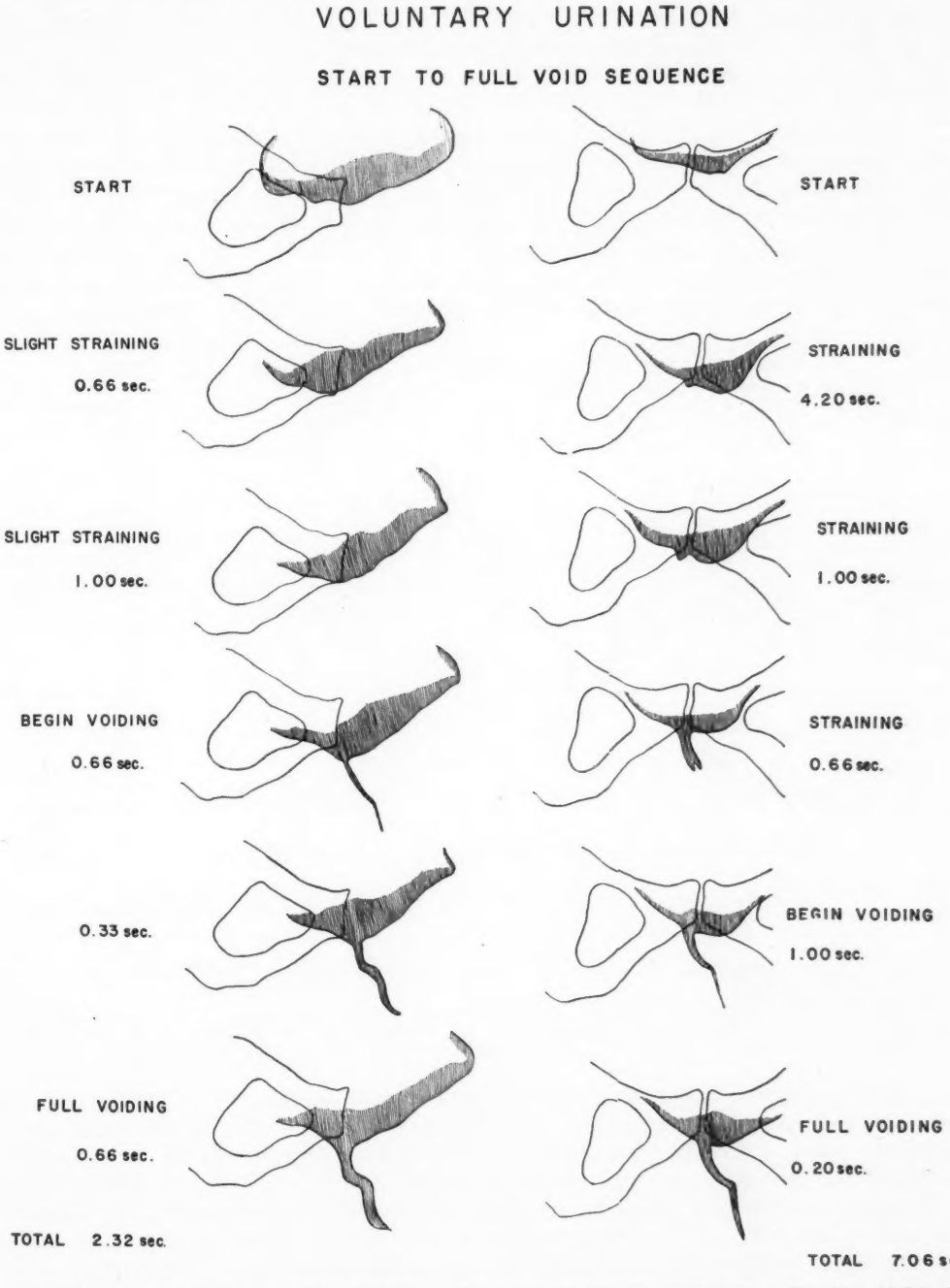


Fig. 2.—On the left, No. 329810, para i, aged 39, no cystocele. On the right, No. 408583, para vii, aged 38, small cystocele, oblique views of normal urination. Both patients show descent of the bladder. The absence of an infundibulum and the speed with which voiding begins suggest that there has been little straining by the patient on the left. In contrast the patient on the right requires 7 seconds to begin urination and during this period of straining a long narrow infundibulum is formed. Both patients, when voiding, show the "knee" of the mid-urethra which lies immediately behind the symphysis.

With downward motion of the bladder the proximal urethra appears to be "shortened." Whether this is an artifact or not is unclear at the moment. In most patients the urethra curves slightly upward toward a "knee" (Fig. 2), from which it bends downward toward the external urethral meatus. The "knee" has not been accurately located; however, it apparently lies immediately behind the symphysis pubis at the junction of the proximal two thirds and distal one third of the urethra. It is the only fixed point which we have observed. The voluntary constrictor fibers lie just proximal to the "knee."

Urination: The silhouette of the urethra varies during urination. As voiding continues the infundibulum progressively lengthens and the base of the bladder rises (Fig. 3). As a result the urethra is apparently elongated. The bladder becomes more rounded and the posterior urethrovesical angle is less obtuse.

Upon two occasions a small amount of air was present in the bladder after the contrast medium had been completely expelled. The air continued to outline the infundibulum for at least 2 seconds after the urethra had closed.

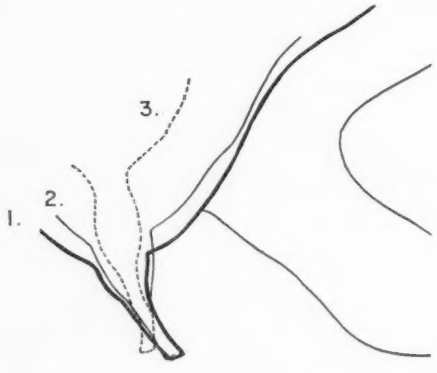


Fig. 3.—Urethrovesical segment during urination. Oblique view. No. 19047, aged 49, multipara without incontinence. The base of the bladder rises progressively as the bladder empties. The urethra is fixed distally and appears to lengthen proximally.

Interruption of urination: When urination is voluntarily interrupted upon command, two events take place. The first is an elevation at the base of the bladder, most noticeable posteriorly. The second is the nearly simultaneous interruption of the stream in the region of the "knee" (Figs. 4, 5). As the lumen of the mid-urethra is quickly obliterated the urine is injected back into the infundibulum. The infundibulum will usually persist until voiding is resumed. If voiding is not promptly resumed the infundibulum slowly disappears.

Involuntary Urination.—Coughing and straining may produce involuntary loss of urine. Escape of a few drops in this manner is not uncommon and it has been suggested that at least half of all women experience this at some time.[11, 12] For this reason we do not consider it to be abnormal. The term *involuntary*

urination is preferred as this incontinence may be "normal" or excessive. When involuntary urination becomes excessive, it may be defined as "stress incontinence."

Cough: Fig. 5 illustrates the changes following a cough. These occur with astonishing speed and the entire act is usually completed in one second. The impact of a cough produces a sudden sharp depression of the base of the bladder. Simultaneously an infundibulum appears. If the patient is "normal"

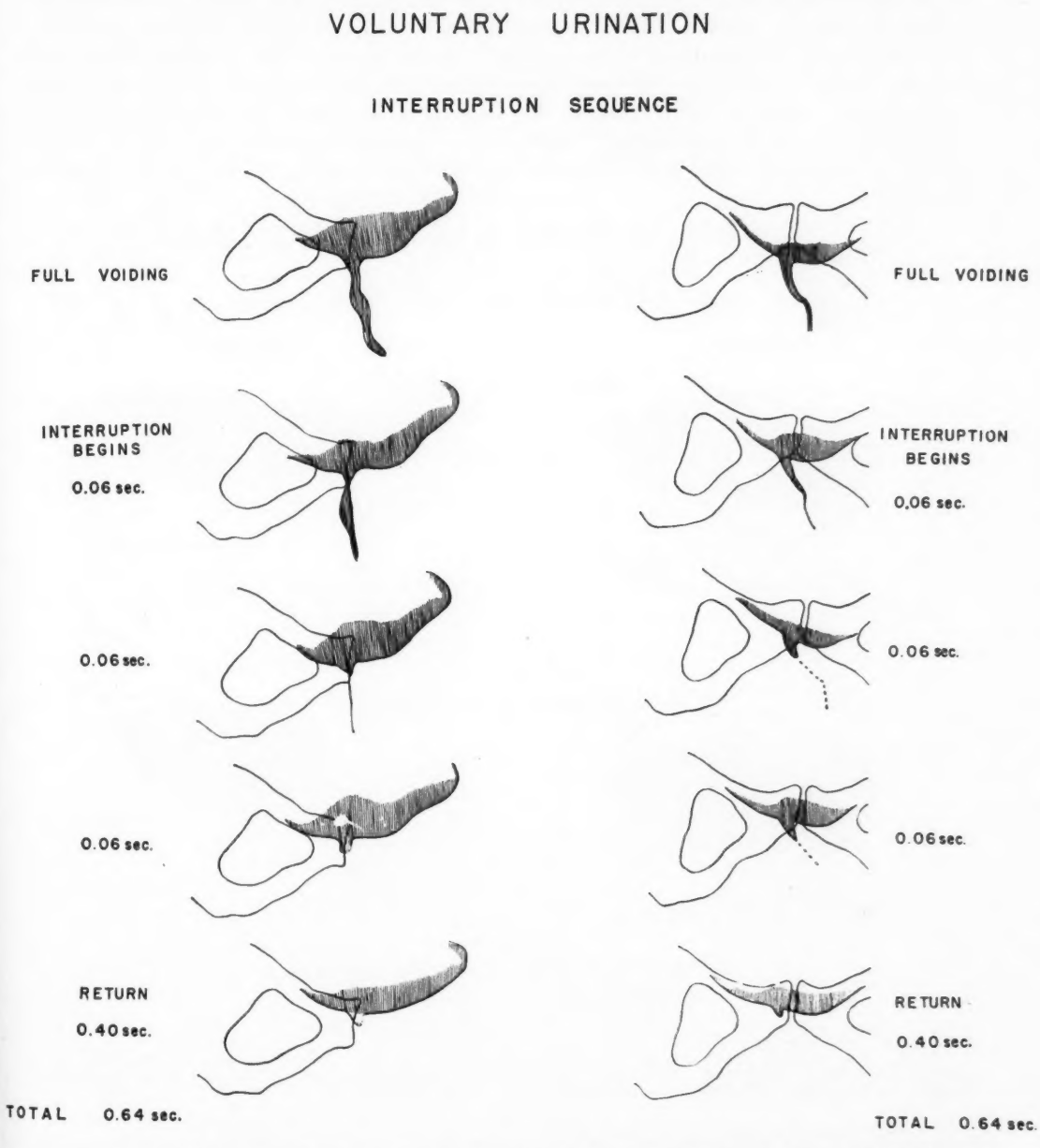


Fig. 4.—Oblique view of same normal patients seen in Fig. 2, showing interruption of urination at identical time intervals. Constriction begins in mid-urethra at the proximal region of the "knee." Simultaneously the bladder base rises. Patient on the right shows the posterior segment to rise first. The urine in the proximal urethra is returned to the bladder. Only a very small infundibulum remains as the resting stage is reached.

this outpouching is usually of small caliber and shallow. In one normal patient it reached the mid-urethral region. After the impact of the cough passes, the infundibulum disappears, the urine returns to the bladder, and the bladder base rises. This infundibulum has been a constant finding and indicates that a small amount of urine has entered the upper urethra without being voided.

If the woman has stress incontinence the introduction of 150 ml. of fluid into the bladder may produce a blunt cone or funnel in the base of the bladder (Figs. 6 and 7). As the impact of a cough develops, the cone becomes broader, descends, and an infundibulum appears at the apex. The column of liquid moves further down the urethra, passes the voluntary constrictors just proximal to the "knee," and escapes involuntarily through the urethral meatus. Immediately, as the maximum impulse of the cough is passed, the urine is injected back into the infundibulum in a manner similar to that of the normal patient.

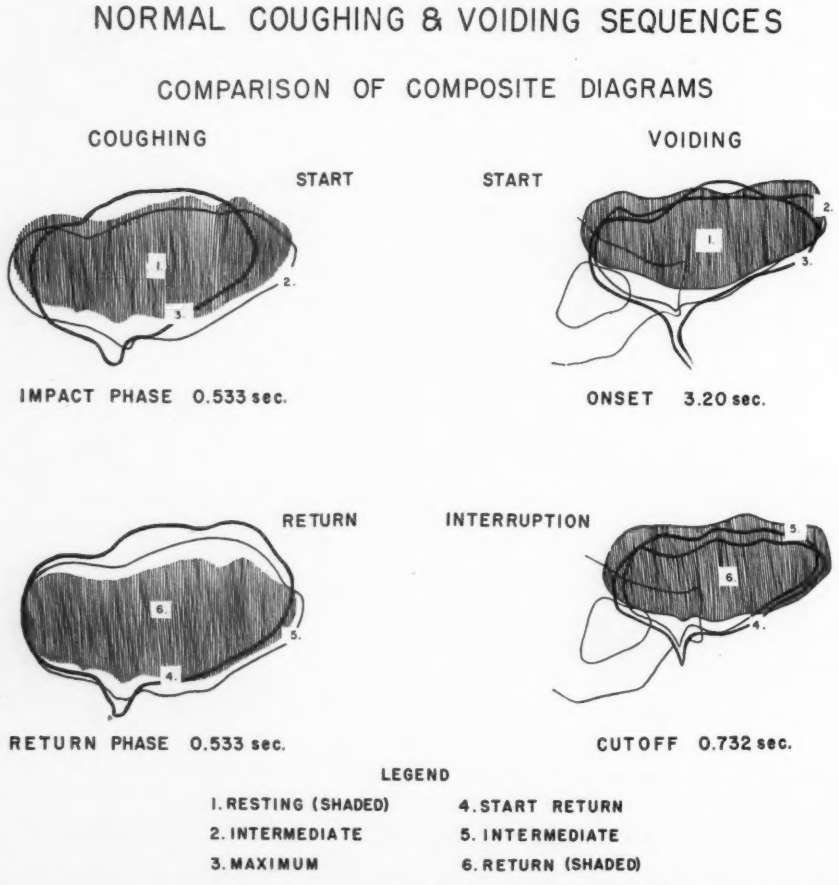


Fig. 5.—Oblique view, bladder and urethra. No. 329810, aged 39, para 1, normal. The bladder becomes round as coughing and voiding begin and the posterior wall descends. Coughing produces a larger infundibulum than does voiding.

Strain: Straining may produce many of the changes that are produced by coughing. The time factor is slower; therefore, individual changes are less striking and the total effect of the action is more difficult to appreciate. If single frames only are analyzed it would be difficult to distinguish the effects of

coughing from those of straining. The base of the bladder descends, an infundibulum forms, and if the voluntary constrictors of the urethra are incompetent urine escapes.

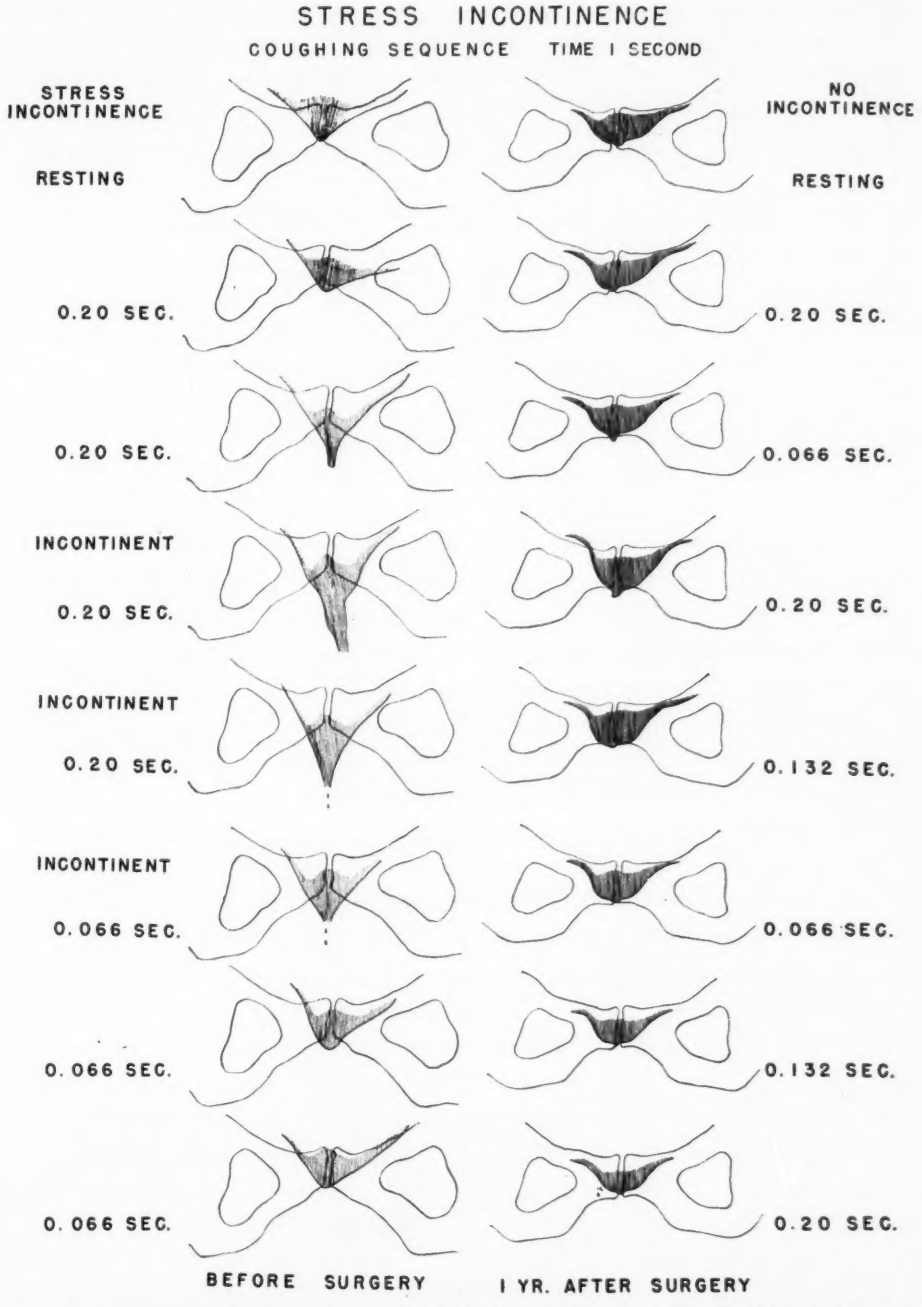


Fig. 6.—Anterior-posterior views. No. 19047, para iii, aged 48. Left-hand frames show moderately severe stress incontinence before surgery, while the right-hand column shows the condition one year after successful surgical correction. The time intervals are approximately the same. In the presence of stress incontinence the base is cone or funnel shaped when the bladder is partially filled. A slight impact further distends the urethrovesical segment, allowing urine to reach and pass the voluntary muscles which are also incompetent. Surgical correction by urethral plication and anterior repair (at this time vaginal hysterectomy) supported the bladder laterally, reduced the cone to a broad, curved base and increased the resistance of the urethrovesical segment so that effort produced only a small infundibulum.

Urination: Except for the cone-shaped bladder base previously described there is little difference between the full voiding stage of micturition of patients who are incontinent and those who are not.

Interruption of urination: Patients with stress incontinence of urine are able to interrupt urination (Fig. 8). Two differences can be seen when comparison is made with the normal. The time interval for voluntary closure of the urethra in 2 patients with stress incontinence was twice as long as that observed in normal patients. The second difference concerns the base of the bladder which rises *after* the voluntary constriction of the urethra.

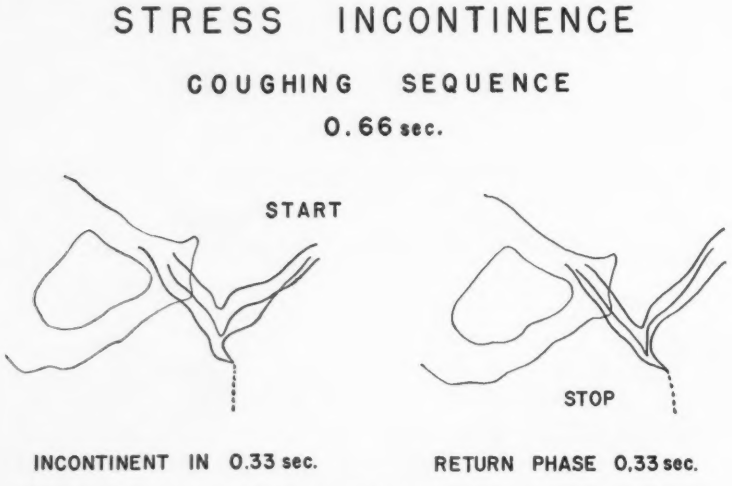


Fig. 7.—Oblique view. No. 292115, aged 36, para iii, stress incontinence. At rest the base of the partially filled bladder exhibits a distinct cone shape with a small infundibulum at its apex. The stress of a cough broadens the cone and forces it downward. The infundibulum also descends. The urine reaches and passes through the voluntary sphincter and the patient becomes incontinent. As soon as the impact is over (0.33 second) the escape of urine ceases and the urethra returns the remaining contents into the bladder. The urethra appears to shorten with the cough and lengthen with return.

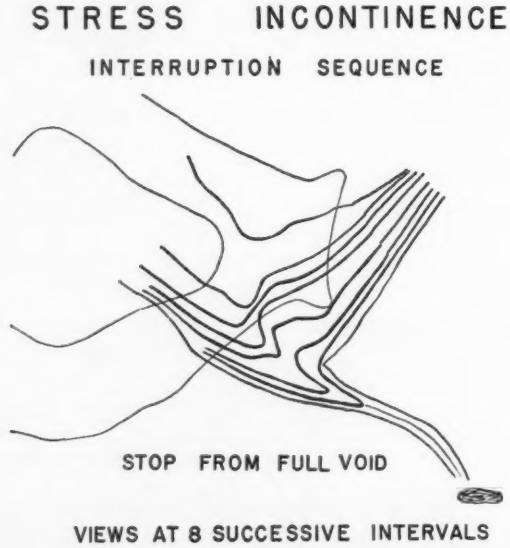


Fig. 8.—Oblique view of patient in Fig. 7. She is able to "cut off" urinary stream on command. The interruption begins in the voluntary segment and precedes the elevation of the bladder base by 0.8 second compared with the normal in Fig. 4. The normal time for interruption is about 0.65 to 0.70 second. In this patient it was prolonged to 1.6 seconds.

Comment

Once upon a time four blind men from India described an elephant. The first one felt the leg and thought the animal was like a tree. Another sat astride and said the beast resembled a hill. The third felt the trunk and believed the elephant to resemble a snake, while the fourth thought the tail was like a duster. So it is with micturition. Different features have been observed and described by nearly every investigator. If the riddle of micturition is to be solved these diverse features must be unified into a complete picture. Cinefluorography offers an excellent medium for such a resolution.

The bladder and urethra are active and dynamic. The term "resting stage" is a misnomer if it implies a static condition as the bladder and urethra move and change position with respiration, position, activity, filling, and emptying. Many of the earlier attempts to analyze function were based on rigid and stereotyped concepts of angles, direction, pressures, etc. There are an infinite number of these and each depends upon the state of the bladder and urethra at the moment of observation. We have observed but one fixed point in this area, the "knee." It lies immediately behind the symphysis pubis and probably represents the attachment of the strong pubourethral ligaments.

It is not easy for anyone to void upon command in front of a motion picture camera. Eighty per cent of our patients did and many of them voided without hesitation or strain. Normal urination starts quickly without hesitation or strain within a second or two. In free voluntary urination, the posterior base of the bladder moves downward and the infundibulum, if present, is small and shallow. The prompt relaxation of the voluntary external constrictors probably prevents the formation of an infundibulum. When the voluntary constrictors fail to relax promptly, continued straining produces an infundibulum. It appears that the size of the cone and the infundibulum depends upon the total intracystic pressure and the resistance of the involuntary muscles and connective tissue of the urethrovesical segment.

Interruption of urination, whether the patient is continent or incontinent, is invariably associated with a voluntary closure of the mid-urethra and a reflux of urethral contents into infundibulum. Ardran[3] has observed this and we have confirmed his findings without exception. An exception might be anticipated if there is neurological disease or total incontinence. We have not studied such patients. The second feature of interruption is the elevation of the base of the bladder. Normally this begins just before or with the urethral constriction. In the incontinent patient elevation lags behind constriction.

Normal voiding is accompanied by marked rise of the bladder as it empties. As the bladder rises the urethra must elongate in some manner because the proximal end is fixed at the "knee." Elongation probably takes place in the area of the urethrovesical junction. We have been impressed with *passivity* of this segment which is quite different from the activity of the mid-urethra. We suspect that there is no functionally specific internal sphincter.

Instead of a sphincter there is probably a region of contractility which is normally kept closed by the integrity of the smooth muscle and surrounding connective tissue. If the bladder is full and there is superimposed impact of coughing, laughing, or other effort, the resistance is overcome and a small quantity of urine enters the involuntary segment. If the force is sufficient we have observed the column of urine to reach the voluntary sphincter. We have not observed escape of urine past the voluntary constrictors in normal women but obviously it must if nearly half of them at some time experience a small amount of involuntary urination under such conditions.

No conclusions can be drawn for this study about the basic lesion or lesions of stress incontinence. Our observations confirm the presence of a cone or funnel in the urethrovesical area. This possibly indicates loss of soft tissue resistance and whatever resistance remains is readily overcome by the increased pressure of effort. Under such conditions urine is present in the upper urethra. The voluntary constrictors offer the only remaining defense against involuntary urination. One may speculate that stress incontinence occurs when the combined resistance of the voluntary and involuntary areas falls below a certain minimal level. Thus a high degree of competence at either level might in itself be sufficient to prevent significant stress incontinence.

Summary

Cinefluorography has been adapted to the study of the bladder and urethra in women. From 500 to 2,000 frames can be made for each patient. Projection of these motion pictures provides a new technique for the study of normal and abnormal urination. Further study will be necessary before the method can be applied clinically.

References

1. Ullery, J. C.: Stress Incontinence in the Female, New York, 1953, Grune & Stratton, Inc.
2. Hodgkinson, C. P.: Am. J. Obst. & Gynec. **73**: 518, 1956.
3. Ardran, G. M., Simmons, C. A., and Steward, J. H.: J. Obst. & Gynaec. Brit. Emp. **63**: 26, 1956.
4. Ardran, G. M., Hamill, J., and Simmons, C. A.: Proc. Roy. Soc. Med. **49**: 647, 1956.
5. Jeffcoate, T. N. A., and Roberts, H.: Surg., Gynec. & Obst. **98**: 743, 1954.
6. Jeffcoate, T. N. A., and Roberts, H.: Proc. Roy. Soc. Med. **49**: 652, 1956.
7. Muellner, S. R.: Surg., Gynec. & Obst. **88**: 237, 1949.
8. Muellner, S. R.: J. Urol. **65**: 805, 1951.
9. Benjamin, J. A., Joint, F. T., Ramsay, G. H., Watson, J. S., Weinberg, S., and Scott, W. W.: Trans. Am. A. Genito-Urinary Surgeons **46**: 43, 1954.
10. Hinman, F., Miller, G. M., Nickel, E., and Miller, E. R.: Radiology **62**: 713, 1954.
11. Nemir, A., and Middleton, R. P.: Am. J. Obst. & Gynec. **68**: 1166, 1954.
12. Duncan, A. S.: Quoted by Kellar, R. J.: Proc. Roy. Soc. Med. **49**: 657, 1956.

Discsussion

DR. HOUSTON S. EVERETT, Baltimore, Md.—I have seen Dr. Marchetti's still x-ray illustrations demonstrating the function of the bladder before and after the Marshall-Marchetti operations, and somewhat similar ones in Jeffcoate's clinic in Liverpool and again in Manchester. From the material in hand I was not too greatly impressed until I had the opportunity yesterday afternoon of viewing the film, which I find simply fascinating.

Dr. Lund and his co-workers have presented us with a masterful piece of physiologic research. I doubt, however, that the method presented will prove of clinical value in the study of individual patients. In the first place, the equipment, labor, and time required would rather render the method too expensive for such application. In the second place, our radiologists have told me that the roentgen rays used for the study of each of these patients have been essentially one-half of a skin erythema dose.

These drawbacks, in so far as clinical usage is concerned, do not detract from the method's potential value for physiologic investigation. The work as presented deals with only two types of patients: those with normally functioning bladders and those with stress incontinence. To me several problems occur which might be further elucidated by the application of this method, and I have no doubt that the authors intend to make such investigations in the future.

Among these problems let me mention first that there are two groups of patients who suffer from stress incontinence. In the larger group there is demonstrable cystourethrocele, and in this group adequate repair of these defects with a plicating stitch or two underneath the proximal urethra usually corrects the incontinence. In the smaller but more troublesome group the women are often nulliparous and there is no demonstrable cystocele or urethrocele. In such patients the vaginal approach is usually completely ineffective in correcting incontinence, and resort must be had to such procedures as the Aldridge strap operation or the Marshall-Marchetti procedure.

Another problem which has always puzzled me is why patients with urge incontinence resulting from a motor type of neurological lesion, such as occurs with spina bifida occulta or multiple sclerosis, have residual urine. As is well known, such patients may have a bladder capacity of only 150 to 200 c.c. and a residual urine of about 100 c.c. On purely theoretical assumption, I have always felt that motor stimuli similar to those which cause frequent contractions of the detrusor muscle with expulsion of small amounts of urine lead to contraction of the sphincters and stoppage of the stream as soon as the intravesical pressure has been partly reduced. This problem certainly deserves further investigation by any available means.

Another problem which occurs to me would be to investigate a patient who is to be treated by Kegal exercises before the beginning of treatment and then, provided the treatment proved successful, after completion of treatment.

This list of problems could be greatly extended but I shall mention only one other, namely, the patients emphasized a few years ago by Dr. Thornton, Dr. Meigs, and others who, after radical hysterectomy and pelvic lymphadenectomy for carcinoma, go for weeks, months, or even years without recovering the ability to void normally.

I have just one small criticism of the technique described. If I understand Dr. Lund corectly, usually only about 200 c.c. of fluid has been introduced into the bladder before the exposures have been begun. The normal capacity of the bladder is approximately 500 c.c., and many patients with slight or even moderate degrees of stress incontinence do not experience leakage until the bladder contains more than 200 c.c. I wonder if a more accurate study might not be obtained if the bladder were filled to more nearly normal capacity.

DR. JOHN A. BENJAMIN, Rochester, New York.—The region about the bladder neck and adjacent urethra has been of interest to the urologists, too. I would like to show you briefly an x-ray motion picture in which one sees the change in the bladder-neck function after the bladder neck was used to replace the prostatic urethra following radical perineal prostatectomy. I feel that the results of our studies of bladder and urethral functions by cinefluorography in both sexes indicate that the bladder neck and the adjacent urethra have more of a physiological role in the so-called internal sphincter action than we have previously supposed. Furthermore, there is a marked similarity between the appearance of the bladder neck and the adjacent urethra in the male with incontinence or involuntary urination when compared with those of the female with involuntary urination.

DR. LUND (Closing).—I think we should have to agree with Dr. Everett that this method is not yet ready for general clinical use. However, I am not at all pessimistic. I believe that the time will come when this will be of clinical use in the assessment of urinary incontinence.

We appreciate the helpful and challenging list of problems which Dr. Everett has proposed. The reason that we used an intermediate amount of opaque medium in the bladder was to avoid production of an abnormal situation. If you are familiar with the literature in this field, criticisms are made if the bladder is too full or too empty, if it is filled too quickly or too slowly, or if the fluid is too warm or too cold. In an effort to keep this at a modest level we have used smaller amounts. Our future studies will include both larger amounts and smaller amounts of fluid.

Case Reports, New Instruments and Methods

PREGNANCY AND Ac-GLOBULIN DEFICIENCY

Report of a Case

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IN THE twelve-year interval between the time Owren[1] first described a case of Ac-globulin deficiency† and Owen[9] made his extensive search of the literature, only 7 cases of symptomatic deficiency of this factor have been reported in women of childbearing age.[1, 10-14] Further search by us has brought to light only one other.[15] Of these 8 women, mention is made of only 3 having become pregnant.[13, 15] We have had the opportunity of following through pregnancy and delivery the patient whose case was originally reported by Alexander and Goldstein.[14] It is the purpose of this report to present the clinical and hematologic findings observed during her pregnancy, delivery, and puerperium.

The patient was a 21-year-old white woman of Italian extraction, who first demonstrated hemorrhagic phenomena at the age of 5 when she required blood transfusion for posttonsillectomy hemorrhage. The tendency to bleed excessively was apparent following tooth extractions, during frequent epistaxes, and after the menarche, when she experienced profuse and prolonged menses. As symptoms, the patient had a sense of fatigue, dyspnea on exertion, and occasional giddiness.

When she was 17 years old, the diagnosis was made of severe congenital Ac-globulin deficiency as well as mild hypoprothrombinemia.[14] (Two siblings at the same time were found to have Ac-globulin deficiency, but of a degree insufficient to produce symptoms.) Investigation disclosed that a definite improvement in the clotting and the bleeding time

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†Synonyms of Ac-globulin—AcG—(Ware and Seegers[2]) are pro-prothrombinase, Factor V, and parahemophilia (Owren[3, 4]); labile factor (Quick[5]); proaccelerin (Astrup[6]); accelerator (Fantl and Nance[7]); plasmatic cofactor of thromboplastin—CPT (Honorato[8]).

occurred both in vivo and in vitro following the provision of Ac-globulin.[14] From the time of diagnosis until the pregnancy three years later, the patient's menorrhagia, which had become the outstanding difficulty, was treated by the infusion of 150 to 300 ml. of fresh frozen plasma at the beginning of her periods. This resulted in a decrease in the amount of the flow but did not shorten the menses.

During pregnancy no bleeding per vaginam was noted, and the patient was brought to term in an uneventful manner.

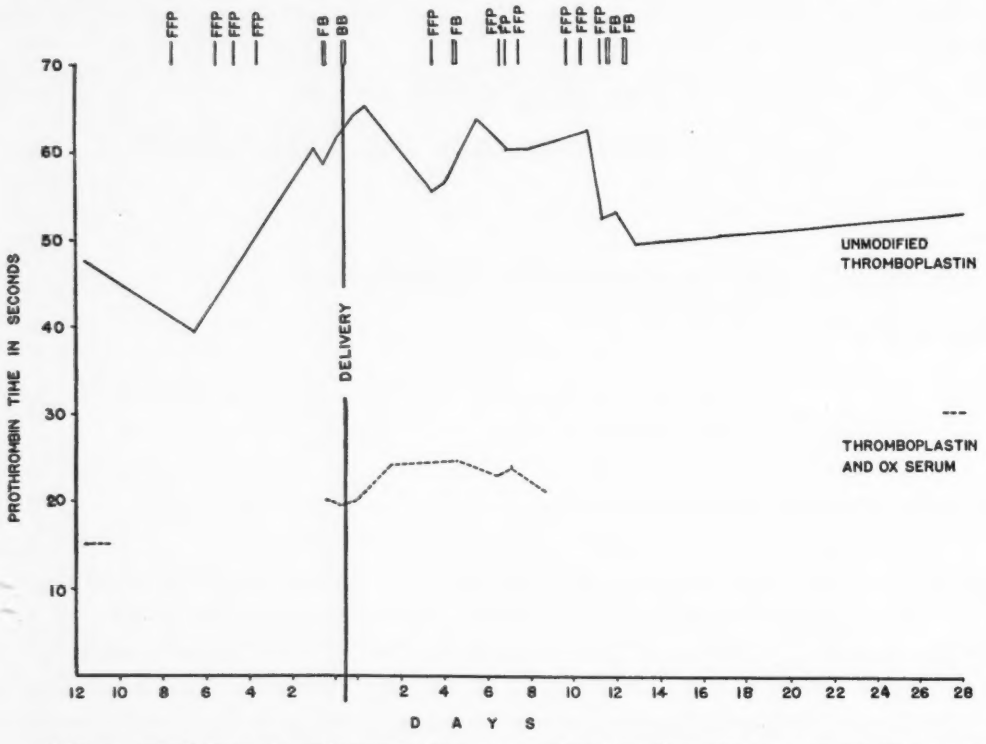


Fig. 1.—Variations of prothrombin time and modified prothrombin time in relation to the delivery and the administration of blood and/or plasma (*FFP*, fresh frozen plasma; *FP*, fresh plasma; *FB*, fresh blood; *BB*, bank blood).

Clinical Course and Laboratory Findings.—The patient was seen at this laboratory eleven days before delivery. Examination showed a hemoglobin of 11.9 Gm., and a normal white blood count and differential. The prothrombin time* was 47 seconds. The same test (hereafter described as "modified prothrombin time") performed with thromboplastin modified with ox serum† was 15 seconds. The blood group was O, Rh factor CDec. With a view to raising the prothrombin time before delivery, 300 ml. of fresh frozen plasma were given. The following day the prothrombin time was found to be 39 seconds; accordingly, six times during the remaining ten days before admission, the patient received infusions of 150 ml. of fresh frozen plasma.

At the time of admission physical examination showed no unusual features. The blood pressure was 110/70; pulse 80; temperature 97.4° F.; respirations 20. Laboratory findings at this time are shown in Table I and Fig. 1.

In the hope of preventing excessive hemorrhage during delivery the patient was given 1,000 ml. of fresh whole blood. As antepartum medication she received a total of

*Quick's one-stage procedure using Difco thromboplastin.[16]

†In this test the thromboplastin solution is modified by adding one-thirtieth of its volume of ox serum deprothrombinated with barium sulfate. The rest of the procedure is similar to Quick's one-stage prothrombin determination.[16]

200 mg. of Demerol and 1/75 grain of scopolamine. Vertex delivery was effected 36 hours from the onset of labor which followed artificial rupture of the membranes. Episiotomy incision and outlet forceps were used. Anesthesia was obtained with oxygen-ether. During delivery the patient received 500 ml. of blood 15 hours old, 10 units of anterior pituitary extract, and 1/320 grain of Ergotrate. No unusual degree of bleeding occurred either at the time of delivery or immediately thereafter. Following delivery the blood pressure was elevated to 160/104 for approximately 1 hour.

Three hours post partum, tests of the clotting mechanism were unchanged except for the clotting time, which was prolonged to 36 minutes. Little change was also noted over the next five days, except for shortening of the modified prothrombin time to 17 seconds. The lochia during this period varied between an estimated 5 and 10 ml. of blood daily, and convalescence was otherwise uneventful. The patient received 1/320 grain of Ergotrate three times a day for three days, and 5 mg. of stilbestrol three times a day for four days. On the sixth postpartum day the patient experienced increasing pain in the left buttock and perineum. A hematoma of moderate size, which drained spontaneously, was noted at the site of the episiotomy the following day. On the fifth day the patient received 150 ml. of fresh frozen plasma, and on the sixth, 500 ml. of fresh blood.

TABLE I. SOME OF THE HEMATOLOGICAL VALUES OBSERVED BEFORE AND AFTER THE PARTURITION

	BEFORE DELIVERY		AT	AFTER DELIVERY		
	DAY 11	DAY 1	DELIVERY	DAY 2	DAY 7	DAY 28
Hemoglobin (Gm. %)	11.9	12.3	15.5	12.7	12.1	13.3
Hematocrit (%)	–	40	46	42	39	43
Leukocyte count	6,750	–	–	–	8,500	6,450
Bleeding time (minutes)*	–	3	3	–	–	2:30
Clotting time (minutes)†	–	33	36	–	–	22
Clot retraction (hours)	–	3	2:30	–	–	2:30
Prothrombin consumption (seconds)‡	–	55	54	80	–	>180
Fibrinogen (dilution)§	–	1/1,600	–	–	–	1/400
Serum calcium (mg. %)	–	10	–	–	–	–

*Duke.

†Lee-White.

‡Coagulation interrupted with sodium citrate one hour after its initiation; a one-stage prothrombin time determination is then done on the serum.

§Serial dilutions of whole blood in Ringer's solution.[12]

Blood findings for the period from the sixth to the tenth day post partum are shown in Table I and Fig. 1. Five hundred milliliters of fresh blood were administered on the tenth postpartum day, which was the day of discharge.

Following discharge to her home, the patient noticed an increase in the amount of lochia, which she described as consisting of dark clotted blood increasing from 4 to 10 "cups" per day. Each of the two days she was at home she received 300 ml. of fresh frozen plasma. On the eleventh postpartum day the hemoglobin was 11.3 Gm. per cent.

On the thirteenth postpartum day the patient began to pass copious amounts of blood per vaginam, and she was admitted to the hospital in a state of moderate shock. The pulse rate was 130; blood pressure 120/60; hemoglobin 10.2 Gm. per cent; hematocrit 30 per cent; clotting time 35 minutes; and clot retraction 3 hours. The patient was given 450 ml. of fresh frozen plasma without response. Marked clinical improvement followed the administration of 1,000 ml. fresh whole blood, however, and the remainder of her second admission was uneventful. During this time she was given 1/4 grain phenobarbital four times a day and Ergotrate, 1/320 grain three times a day for three days, and a multiple vitamin and mineral preparation. Coagulation data during this admission were similar to those obtained prior to discharge.

The last examination of the patient occurred on the twenty-eighth postpartum day. After her release from the hospital she had experienced no unusual complaints and the

lochia, except for minimal staining with blood on one occasion, remained serous in character. Table I shows the laboratory findings at this time. The clotting time and the prothrombin consumption showed marked improvement. Serum paper electrophoresis at this time presented a pattern within normal limits.

The child and the father were also investigated. The infant was a male who weighed 7 pounds, 6 ounces, at birth. No unusual features were noted until the child became icteric on the second day. There was no clinical evidence of hemorrhagic disease and the icterus cleared three days after its onset. The cord blood at delivery showed a prothrombin time of 18.6 seconds, and a modified prothrombin time of 14 seconds. At the height of the icterus the indirect serum bilirubin reached 16.5 mg. per cent. Over a period of four weeks the clotting time varied between 3 and 2 minutes; the prothrombin time was 15.4 seconds; and the modified prothrombin time 14 seconds. His blood group was A, Rh factor CDec.

The patient's husband was 29 years old and of Italian extraction. His health had been excellent at all times and no familial history of abnormal bleeding could be elicited. All laboratory examinations referable to his clotting mechanism were within normal limits.

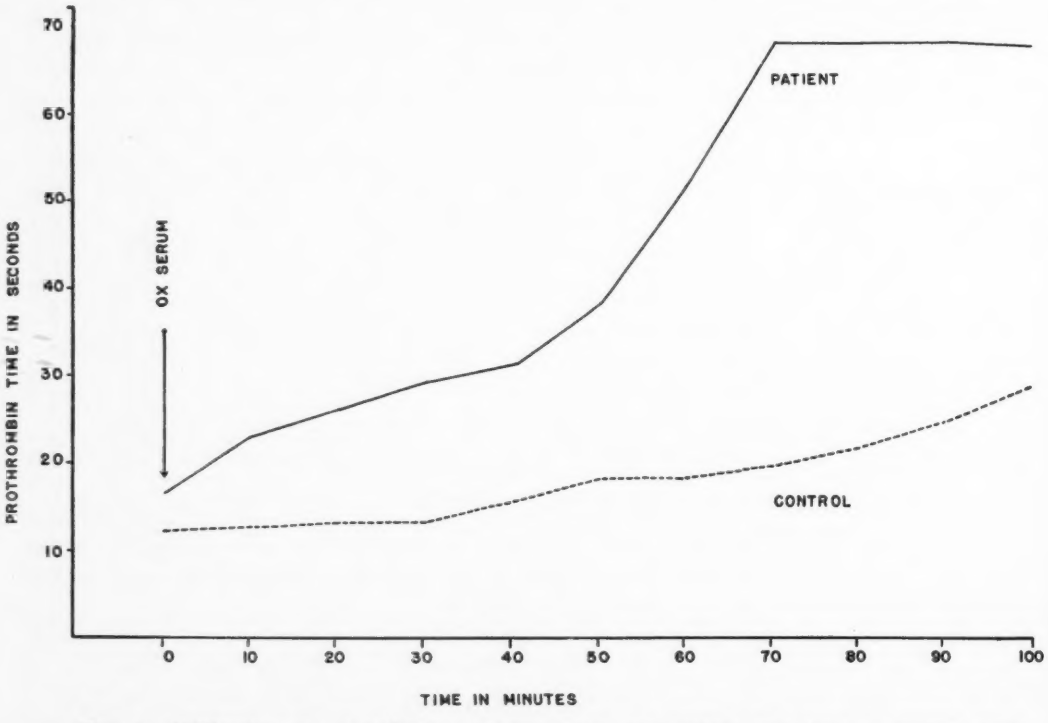


Fig. 2.—Utilization of Ac-globulin. Plasma from the patient and from a control were obtained at the same time and aged at 40° F. for 17 days in order to destroy as much of the Ac-globulin present as possible. Then Ac-globulin, in the form of deprothrombinated ox serum, was added to each and the samples were incubated at 37° C. for 100 minutes during which time serial one-stage prothrombin time determinations were made. The control was a white woman of Italian extraction, of the same age and at the same stage of her first puerperium, whose tests of coagulation were within normal limits.

Comments

The conduct of this patient and of those of Brink and Kingsley,[13] whose patients also had an unremarkable pregnancy and delivery, suggests that, where Ac-globulin deficiency complicates the pregnancy, the prognosis for mother and child may be influenced to a minor rather than to a major degree. Because excessive hemorrhage occurred neither during the pregnancy nor at

the time of delivery, the patient evinced no more concern for herself than many primigravidas who present no such abnormality. The hemorrhage which occurred following her discharge to her home, although possibly related to the clotting defect per se, could be related more closely to her resumption of activity in the presence of the defect. This is suggested by the response of the patient to the routine management of the postpartum hemorrhage.

Comparison of the coagulation tests performed shows that there was no amelioration of the clotting defect during pregnancy. On the other hand, the hematologic findings in the infant suggest that his blood has no such deficiency. Apparently the Ac-globulin present in the fetal circulation was unable to modify the mother's deficiency. The explanation for this phenomenon may be (1) that there was too small a quantity of fetal Ac-globulin crossing into the maternal circulation to change the mother's clotting defect; (2) that the mother may have destroyed fetal Ac-globulin, e.g., by antibody formation; or (3) that the particular protein fraction which contains this globulin does not cross the placental barrier.

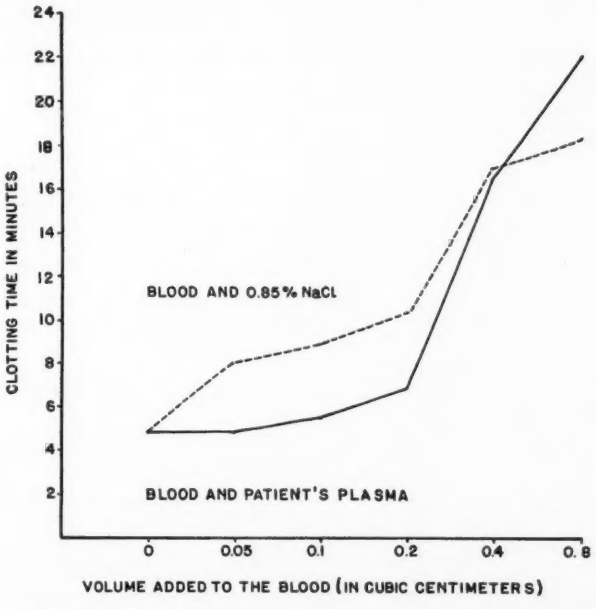


Fig. 3.—Effect of the patient's plasma on the coagulation of normal blood. The blood of a satisfactory normal individual is drawn and immediately placed in two groups of tubes, one containing increasing amounts of plasma of the patient studied, and the other containing increasing amounts of 0.85 per cent sodium chloride. Both sets of tubes contain the same concentration of sodium oxalate.

It is interesting to note that the prothrombin time (Fig. 1) improved several days before and after the delivery, and that this coincided with the administration of large quantities of fresh blood and fresh frozen plasma. Unfortunately, no conclusion can be drawn because the blood and plasma were not checked before administration in every instance for their content of Ac-globulin, or for their ability to modify the patient's plasma in vitro (clot-promoting effect in vitro).

Results from the attempt to demonstrate the presence of a factor or factors that would inhibit Ac-globulin specifically appear to indicate increasing destruction of a coagulation element (Ac-globulin?) in the patient's plasma (Fig. 2). It was noted, however, that the plasma of the patient failed to modify the clotting time of a normal individual (Fig. 3).

As there has been no report as yet of spontaneous cure of congenital Ac-globulin deficiency, a problem presented itself in the further management of this patient. The only real difficulty that this woman has experienced in the past has been menorrhagia. The patient was now in the position where her clotting time no longer returned to normal following the infusion of fresh frozen plasma or fresh blood, and there was the possibility to be considered of fatal exsanguination occurring at the time of menstruation. Because it was felt that menstruation and pregnancy could follow with as few complications as previously, and because this woman was only 21 years of age, the conservative approach to management was favored. This proved to be a fortunate choice because, since this report was prepared, and without benefit of further therapy, the patient has experienced six menstrual periods uncomplicated by severe hemorrhage, and is now in the fourth month of her second pregnancy.

Summary

A patient with congenital parahemophilia has been followed through a relatively uncomplicated pregnancy, delivery, and puerperium. Comments are made upon the hematologic and clinical findings, with regard to considerations of theoretical interest and problems of management.

References

1. Owren, P. A.: Det Nørske Videnskaps-Akademi i Oslo, November, 1944, p. 21.
2. Ware, A. G., Guest, M. M., and Seegers, W. H.: Science 106: 41, 1947.
3. Owren, P. A.: Acta med. scandinav., supp. 194, p. 1, 1947.
4. Owren, P. A.: Lancet 1: 446, 1947.
5. Quick, A. J.: Lancet 2: 379, 1947.
6. Astrup, T.: In Nord, F. F.: Advances in Enzymology and Related Subjects of Biochemistry, New York, 1950, Interscience Publishers, Inc., chap. 10, p. 1.
7. Fantl, P., and Nance, M.: Nature, London 158: 708, 1946.
8. Honorato, R.: Am. J. Physiol. 150: 381, 1947.
9. Owen, C. A., Jr., and Cooper, T.: A. M. A. Arch. Int. Med. 95: 194, 1955.
10. Marx, R.: Ärtzl. Forsch. 4: 567, 1950.
11. deVries, A., Matoth, Y., and Shamir, Z.: Acta haemat. 5: 129, 1951.
12. Stohlman, F., Harrington, W. J., and Moloney, W. C.: J. Lab. & Clin. Med. 38: 842, 1951.
13. Brink, A. J., and Kingsley, C. S.: Quart. J. Med. 21: 19, 1952.
14. Alexander, B., and Goldstein, R.: Am. J. Med. 13: 255, 1952.
15. Hörder, M. H.: Acta haemat. 13: 235, 1955.
16. Quick, A. J.: The Physiology and Pathology of Hemostasis, Philadelphia, 1951, Lea & Febiger.
17. Schneider, C. L.: Am. J. Obst. & Gynec. 64: 141, 1952.

A SIMPLE INSTRUMENT FOR THE DETERMINATION OF THE INTENSITY, FREQUENCY, AND DURATION OF LABOR

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THE search for a means of determining whether or not true labor is present, and to measure the force of uterine contractions during labor, dates back to the middle of the nineteenth century. In 1861 the first attempt to devise an instrument for that purpose was made by Kristeller.[1] He used a spring measuring device attached to an obstetrical forceps. This device was used primarily to determine the amount of force necessary to deliver the baby. Since this time there have been many different means developed to determine the character of uterine contractions. Such instruments have been referred to as tokodynamometers, and they have been used for various purposes, mainly to facilitate delivery, to understand more clearly the underlying physiology of normal and abnormal labor, and to study the effect of various drugs employed during labor and delivery.

These instruments are of 2 types: internal, where the detector is placed within the uterus, and external, where the detector is placed on the surface of the abdomen. We are concerned solely with a simple external instrument.

In 1896 Schaeffer[2] devised the first external apparatus consisting of an air-filled hood with a rubber membrane. In the same year, Bukoemsky[3] developed a Marey tambour attached to the abdominal wall. Since 1913 numerous apparatus have been introduced.[4-9] In 1942 Fenning[10] invented a somewhat complicated "Capacigraph," employing an oscillating vacuum circuit. He later used a simpler apparatus featuring a lever system. All such devices led to the development of more complicated electrical and mechanical apparatus, the latest of which has been the tokodynamometer[11-13] originated in 1947-1948. The TKD works with several leads, and simultaneously records uterine activity at various points on the abdominal wall. The internal tokodynamometers have fallen into disfavor because they involve invasion of the uterus, thus exposing the patient to possible infection.

We now wish to present the following instrument as a simple means of helping to determine the nature of uterine contractions during labor.

The apparatus consists of a semilunar, clear hard plastic yoke, to the ends of which is attached a washable plastic belt to fasten it to the abdomen. Projecting from the center of the yoke is a metal tubular rod which in turn is connected to a diaphragm contained in a round plastic box. The metal rod can be adjusted to different levels in order to

bring the diaphragm in close approximation with the abdomen, thus accommodating to the contour of the abdomen. The other end of the rod is connected by rubber tubing to a kymograph.* The latter records the intensity, frequency, and duration of the uterine contractions (Fig. 1). Note that the tracing consists of vertical lines each representing a minuute, and horizontal lines which indicate the height of the pressure. The apparatus, while in operation, allows sufficient movement of the patient without any untoward effect on the tracing (Fig. 2).

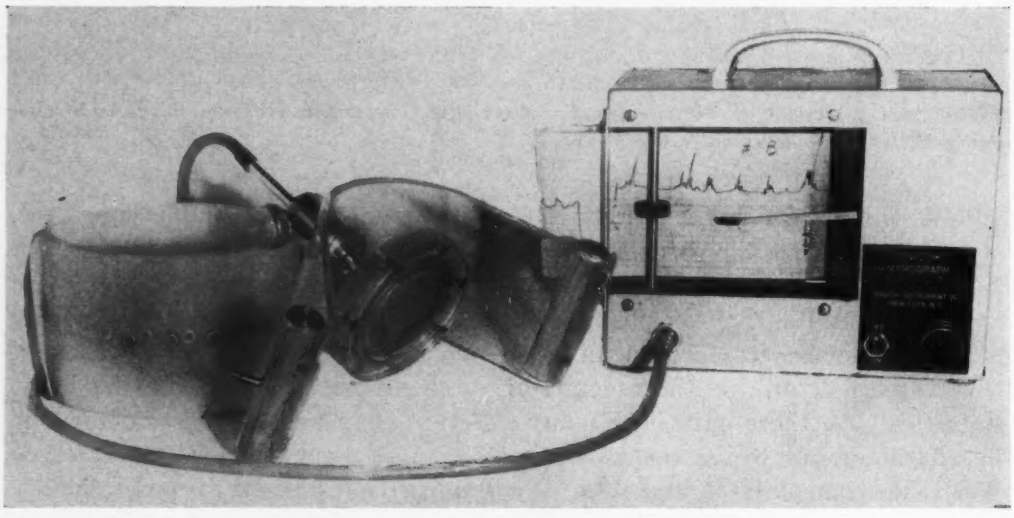


Fig. 1.—Parts of apparatus described in text.

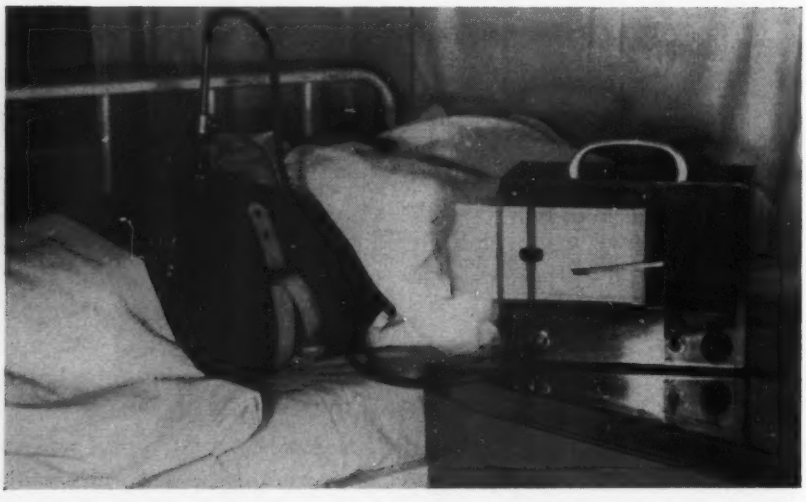


Fig. 2.—Apparatus in operation attached to patient.

A recorded graph of uterine contractions in the last 50 minutes of normal labor in a multiparous patient is represented in Fig. 3. The contractions are regular, occurring every two to three minutes, and are of high amplitude. The close multiple vertical lines at the height of some contractions are respiratory oscillations which seem to occur in some patients. As delivery approaches, the intervals between contractions become extremely regular.

*Kymograph manufactured by the Grafax Instrument Co., New York, N. Y.

Fig. 4 is a tracing of a patient in false labor. For 12 hours she complained of severe intermittent abdominal pains and yet there appeared to be no uterine contractions. Note that the oscillations are almost nonexistent. This patient went into true labor 24 hours later and had a short course of labor.

Fig. 5 represents labor in a primiparous patient with pre-eclampsia which was induced with intravenous Pitocin. Note the irregular contractions in the first few hours. The number of drops per minute was increased and the contractions became more regular. The patient had a short labor and was delivered of a living baby.

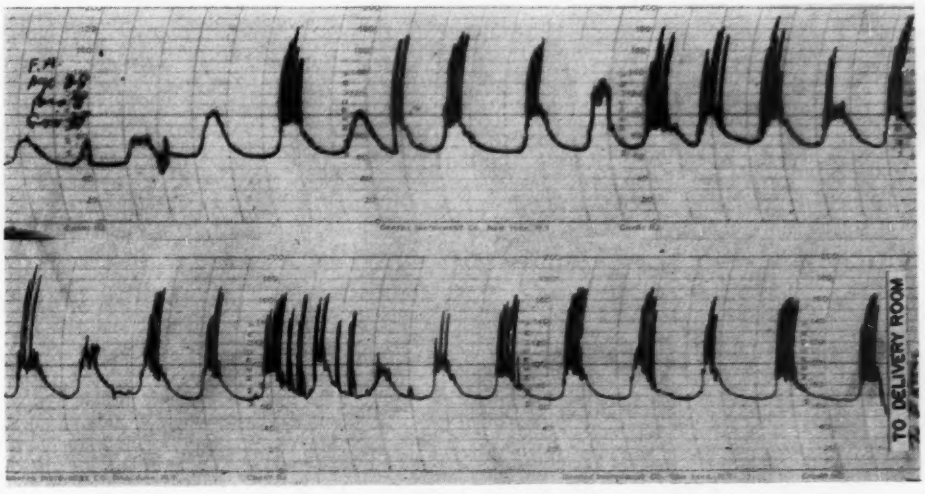


Fig. 3.—Recorded graph of the uterine contractions of normal labor in a multiparous patient during the last 50 minutes before delivery.

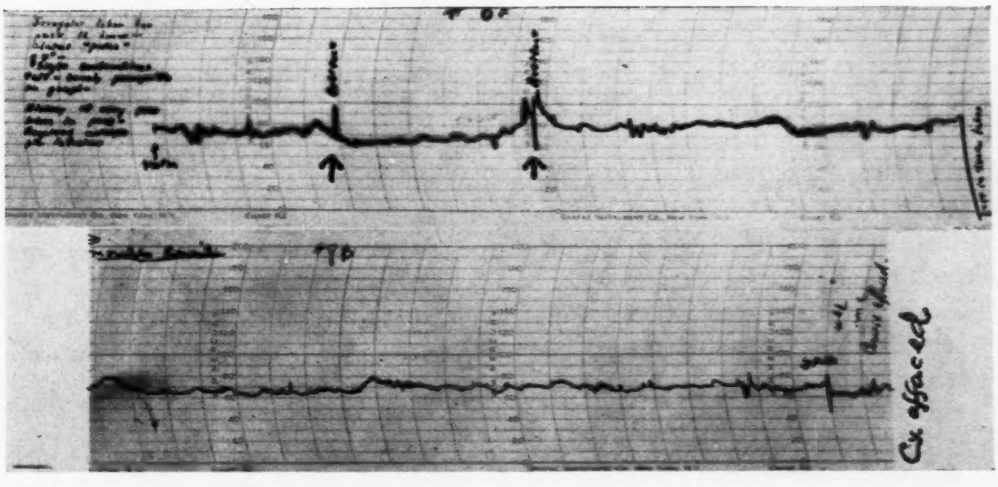


Fig. 4.—Recorded graph of multipara 12 hours in false labor. Arrows indicate artifact.

Comment

With the advent of intravenous Pitocin to induce or augment labor, the obstetrician, now more than ever, is faced with the task of deciding whether a patient has good or poor uterine contractions. At the present time he must rely on subjective symptoms which are unreliable due to varying thresholds

of pain, the periodic and often infrequent observations of a nurse, or his own appraisal of the patient's progress. The scarcity of experienced nurses results in equally inaccurate observations. We hear during discussions at obstetrical conferences the debatable question, "How long was this patient in true labor?"

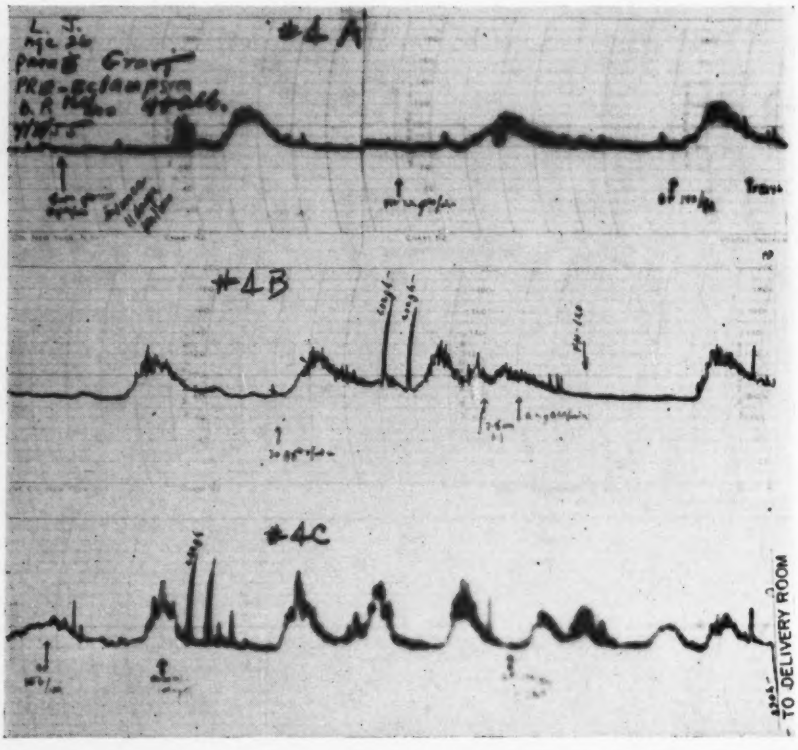


Fig. 5.—Recorded graph of primipara with pre-eclampsia. Labor was induced with intravenous Pitocin. Contractions were irregular for the first 2 hours, but they became regular and of good intensity when the dose was increased to 22 drops per minute. The patient had a short labor and was delivered of a living baby after 3 hours.

A labor recorder is here presented as a simple apparatus to aid the obstetrician in determining the quality of uterine contractions. This instrument is not intended to give a tracing of the complete course of labor, but rather one of the quality of labor at various intervals. It is also possible to observe other phases of labor, such as the development of an abnormal presentation. Further studies with this instrument may also supply us with more information about the physiological mechanism of labor.

Summary

A simple, inexpensive instrument is described which helps differentiate true from false labor. No special training is necessary to operate it. Several graphs have been presented illustrating some of the uses of this apparatus.

References

1. Kristeller, S.: Geburtsh. u. Frauenkr. 17: 166, 1861.
2. Schaeffer, O.: Experimentalle Untersuchungen über die Wentaligkeit des menschlichen Uterus, Berlin, 1896, A. Hirschwald.

3. Bukoemsky, F. W.: Monatsschr. Geburtsh. u. Gynäk. **3**: 197, 1896.
4. Fabre, M.: Bull. Soc. d'obst. et de gynéc. **16**: 68, 1913.
5. Rubsamen, W.: Arch. Gynäk. **112**: 459, 1920.
6. Crodel, W.: Arch. Gynäk. **132**: 23, 1927; Ztschr. Geburtsh. u. Gynäk. **97**: 138, 1930.
7. Dodek, S. M. L.: Surg., Gynec. & Obst. **55**: 45, 1932.
8. Vignes, H.: Biol. méd., Paris **29**: 209, 1939.
9. Vignes, H., Landrieu, R., and Lerouge, J.: Bull. Soc. d'obst. et de gynéc. **23**: 396, 1934.
10. Fenning, C.: Am. J. Obst. & Gynec. **40**: 330, 1940; **43**: 791, 1942.
11. Reynolds, S. R. M., Heard, O. O., and Bruns, P.: Science **106**: 427, 1947.
12. Reynolds, S. R. M., Hellman, L. M., and Bruns, P.: Obst. & Gynec. Surv. **3**: 629, 1948.
13. Reynolds, S. R. M., Heard, O. O., and Hellman, L. M.: Bull. Johns Hopkins Hosp. **82**: 446, 1948.

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PREGNANCY COMPLICATED BY PRIMARY CARCINOMA OF THE OVARY*

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MALIGNANT disease of the ovary complicating pregnancy is rare. Traut and Kuder[1] reported 53 ovarian tumors in 2,300 deliveries, and of these 2 were malignant. Szathmary[2] stated that 5 to 7 per cent of ovarian tumors associated with pregnancy are malignant. In well over 100,000 pregnancies, Gustafson, Gardiner, and Stout[3] collected 45 cases of surgically proved ovarian tumors which measured 6 cm. or larger. One of these 45 tumors was malignant, an incidence of 2.2 per cent. It is interesting to note that all of these figures are well below the 15 per cent malignancy rate that is usually cited[4] for ovarian tumors as a group.

Case reports in the literature are conspicuously few. Bossert[5] was able to collect and tabulate a total of 15 cases, including his own, at the time of his report in 1942. Daro and his associates[6] brought the total number of authentic reports to 19 in 1949. There have also been cases reported by Cunningham and McGrath,[7] Schneider and Vesell,[8] and the 3 cases from the series of Hamilton and Higgins.[9] Falk and Mason[10] reported one case of malignant arrhenoblastoma coexisting with pregnancy. Case reports by Quehl[11] and Gustafson[3] were also found. Greene, Smith, and McClelland[12] reported a case which they believed to represent the only highly malignant granulosa-cell tumor associated with pregnancy; it resulted in the death of the patient in only a few weeks after it had been diagnosed.

The case reports found in the literature number 28. We therefore considered the subject of sufficient interest and rarity to report the following case.

M. K. is a 20-year-old gravida ii, para i, who registered at the Brooklyn Hospital prenatal clinic on Oct. 4, 1955. Her complaints were morning sickness, frequency of urination, tender breasts, and amenorrhea. Her last normal menstrual period was on June 13, and the expected date of confinement was calculated to be March 20, 1956. The menstrual periods had always been regular, occurring every 28 days and lasting 6 days.

Physical examination was normal, except for slight tenderness in the right lower quadrant. The uterus was soft and enlarged to the size of a 14 weeks' gestation. There was the sensation of a mass bulging into the posterior cul-de-sac. This mass was cystic, nontender, about 10 cm. in diameter, and apparently arising from the right side. Stereoscopic x-ray examination of the abdomen did not disclose any evidence of a mass or any calcified area.

*Presented at a meeting of the Brooklyn Gynecological Society, May 16, 1956.

On November 16, during the patient's twentieth week of gestation, an exploratory laparotomy was performed. The right adnexa did not appear unusual. There was a tense, smooth cystic mass which arose from the left ovary and lay wedged in the posterior culde-sac. The cyst was delivered with some difficulty but was successfully removed intact. Grossly the cyst appeared benign, and there was no evidence of metastatic lesions anywhere in the pelvis or abdomen. Frozen section, however, strongly suggested that the tumor was a malignant papillary adenocarcinoma.

The patient's postoperative course was uneventful. She was placed on heavy sedation and was given progesterone intramuscularly for 5 days. On the eighth postoperative day, she was discharged to be followed in the prenatal clinic.

Pathology.—The cyst measured 15 cm. in diameter. Its surface was smooth except for a few protruding nodules. The lining was also covered with yellow nodules resembling frog's spawn. Microscopic examination showed numerous branching, polypoid, and papillary protrusions projecting into the lumen of the cyst. These processes were covered by epithelium. It was of simple columnar structure in places, but in most fields it gave rise to numerous closely-set tiny papillations that formed a corona-like covering of each of the larger polypoid structures. There was only minor variation in size, shape, and staining properties of the epithelial cells and no invasion of the stromal stalks or wall of the cyst. The diagnosis was Grade I papillary serous cystadenocarcinoma of low-grade malignancy with no stromal involvement.

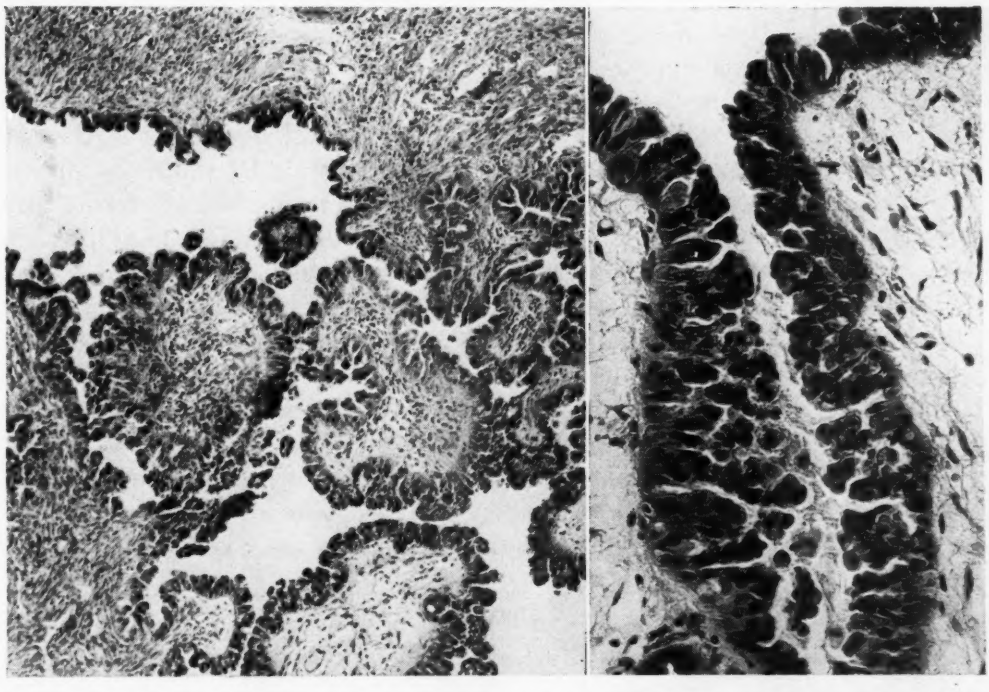


Fig. 1.—Papillary serous cystadenocarinoma, Grade I, removed at the twentieth week of gestation.

Pathological and gynecological consultation at the Memorial Hospital corroborated the opinions of our group. It was recommended that the other ovary be inspected at a second laparotomy at the time of cesarean section near term.

Accordingly, on March 6, 2 weeks before term, the patient was admitted to the hospital. Examination at that time showed the breech in the pelvis and the estimated weight of the baby to be 2,300 grams. Roentgen studies, however, showed no definite

evidence of calcification of the femoral epiphysis. Because of these findings, the patient was discharged and cesarean section rescheduled for March 19, one day before the expected day of confinement.

However, on March 16 at 6 A.M., the patient was admitted in active labor which had started at 4:40 A.M. The cervix was 4 cm. dilated and the breech presenting. Labor progressed rapidly, and it was decided to allow the patient to be delivered vaginally. After a total labor of 3 hours and 20 minutes, she was delivered of a 2,877 gram living female child as a spontaneous breech with assistance.

A laparotomy was performed a few hours thereafter. A frozen section of what proved to be a foreign-body granuloma at the site of the left infundibulopelvic ligament was performed. A wedge resection of the right ovary was also performed. No evidence of new or metastatic growth could be found. The abdomen was closed without further surgery. The postpartum course was uneventful, and the patient was discharged on the tenth postpartum day.

Follow-up examinations for one year postoperatively are normal.

Comment

The prognosis for ovarian cancer cannot be precisely stated because of the varying criteria for malignancy used by different pathologists. The overall 5 year cure rate is 30 per cent at the Sloane Hospital in New York.[13] The 5 year survival rate for papillary serous cystadenocarcinoma is reported as 35.8 per cent. It is in the serous papillary tumors that the histologic type affects the prognosis significantly. In the "borderline" tumor and the Grade I tumor the 5 year survival rate is quoted[13] at 89.8 per cent and 60.8 per cent, respectively. These figures are to be compared with the results in Grade II where the 5 year survival rate is 22.2 per cent, or Grade III where the survival rate is 6.5 per cent. The rate in the above-quoted series was not significantly altered in cases in which only one ovary was involved when a unilateral oophorectomy instead of a bilateral oophorectomy was performed.

We are not advocating conservative treatment for ovarian cancer. Until a better means of evaluation is available, a radical approach should be used wherever possible. When one is faced with the rare problem of a pregnancy complicated by ovarian carcinoma, however, the previously mentioned figures which give only an average prognosis may well be used as a guide for surgery. A hysterectomy and bilateral salpingo-oophorectomy at the time of the initial laparotomy were considered too radical in this case. The cesarean section was to have been carried out for the purpose of re-examining the pelvic organs.

Summary

1. Malignancy is present in about 2 to 3 per cent of the ovarian tumors which occur during pregnancy.

2. Twenty-eight cases of cancer of the ovary in pregnancy were found in the literature.

3. The management of a case of papillary adenocarcinoma in the first trimester of pregnancy in a 20-year-old multipara is presented.

I wish to thank Dr. J. Thornton Wallace and Dr. Arthur T. Antony for their assistance in preparing this paper, and Dr. J. Arnold DeVeer and Dr. J. Edward Hall for help in the interpretation of the pathological specimens.

References

1. Traut, H. F., and Kuder, A.: Internat. Clin. **3**: 285, 1940.
2. Szathmary, Z. V.: Ztschr. Geburtsh. u. Gynäk. **106**: 238, 1933.
3. Gustafson, G. W., Gardiner, S. H., and Stout, F. E.: AM. J. OBST. & GYNEC. **67**: 1210, 1954.
4. Curtis, A. H., and Huffman, J. W.: Textbook of Gynecology, Philadelphia, 1950, W. B. Saunders Company.
5. Bossert, L. J.: AM. J. OBST. & GYNEC. **44**: 336, 1942.
6. Daro, A., Carey, C. H., and Zummo, B. P.: AM. J. OBST. & GYNEC. **57**: 1011, 1949.
7. Cunningham, J. F., and McGrath, J.: J. Obst. & Gynaec. Brit. Emp. **49**: 36, 1942.
8. Schneider, H., and Vesell, M.: AM. J. OBST. & GYNEC. **53**: 688, 1947.
9. Hamilton, H. G., and Higgins, R. S.: Internat. Abstr. Surg. **89**: 525, 1949.
10. Falk, H. C., and Mason, V. C.: AM. J. OBST. & GYNEC. **62**: 1160, 1951.
11. Quehl, E.: J. Obst. & Gynaec. Brit. Emp. **57**: 253, 1950.
12. Greene, G. G., Smith, A. E., and McClelland, T.: AM. J. OBST. & GYNEC. **60**: 686, 1950.
13. Corscaden, J. A.: Gynecologic Cancer, Baltimore, 1951, Williams & Wilkins Company.

A NEW TECHNIQUE FOR THE COLLECTION OF UTERINE CURETTINGS

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CERVICAL dilatation and uterine curettage is one of the oldest and most frequently performed of gynecologic operations. Its chief purpose is to obtain a specimen of endometrial and endocervical tissue for histologic study, and the accuracy of that study parallels the efficacy with which the uterine cavity is curetted. No less important, however, is the transfer of the tissue so obtained to the microscopic slide, and the most competently performed curettement is of little avail if the bulk of the tissue obtained is lost in the transfer from the cervical os to the specimen bottle. The occasional "dry" curettement is a source of embarrassment to gynecologist and pathologist alike.

The standard description of the collection of uterine curettings provides for the placement of a piece of gauze between the cervix and the weighted vaginal speculum and the deposition of the tissue and blood obtained from the uterus on its surface. In favorable instances the unclotted blood soaks into the interstices of the gauze while the endometrial tissue remains on its surface. These tissues are then transferred to the specimen bottle by a gentle scraping motion. When the curettings are scant, however, it not infrequently happens that they too become enmeshed in the gauze and cannot readily be transferred to the specimen bottle. Sending the impregnated gauze to the laboratory merely transfers the process of mechanical separation to another room but does not eliminate the possible loss of vital portions of the specimen.

This difficulty has of course long been recognized and an alternative method provides for collection of the specimen on a piece of rubber dam. While scanty curettings are thus preserved, they may readily be lost in the accompanying blood which then has an opportunity to clot around the fragments of endometrial tissue.

Within recent years a new dressing product called Telfa* has appeared on the market, intended for application to oozing wounds. This material consists essentially of a thin sheet of perforated plastic film backed by a layer of absorbent cotton. In practice its ready separation from bleeding wounds is due to the fact that unclotted blood enters the absorbent layer through the perforations in the nonabsorbent plastic. It occurred to us that this property made this material peculiarly suitable for the collection of uterine curettings since the unclotted blood could readily pass through the perforated plastic layer while the endometrial tissue would not.

*Telfa is manufactured by Bauer & Black, a division of the Kendall Co., Chicago, Ill.

The technique for use of this material following dilatation of the cervix is to place it shiny side uppermost between the cervix and the weighted vaginal speculum. The curettings are allowed to fall gently on the Telfa and the blood can be seen to pass through the perforations into the cotton backing. If bleeding is profuse it is sometimes desirable to place an ordinary gauze pad beneath the Telfa strip to increase its capacity for blood saturation. If desired, separate strips can be used for the cervical and the corpus portions of the curettage. Following completion of the procedure the strip is carefully withdrawn and the collected curettings may readily be transferred to the specimen bottle by any blunt instrument, preferably the handle of an ordinary scalpel. This technique has been employed in an informal test by many of my colleagues who have reported great satisfaction with it. In some instances it made the difference between a small but satisfactory specimen and no specimen at all when the curettings were minimal.

CENTRAL PLACENTA PREVIA ACCRETA

A Case Report

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PLACENTA accreta is the abnormal invasion of the uterine wall by the chorionic villi. This diagnosis must be confirmed microscopically. Placenta previa accreta is the concurrence of placenta previa and placenta accreta.

Incidence.—It is impossible to obtain the statistical incidence of placenta previa accreta; only 40 case reports appear in the literature. The incidence of placenta accreta itself varies with the authority quoted. Irving and Hertig[5] reported an incidence of once in 1,956 deliveries at the Boston Lying-in Hospital; Kraul[10] reported 3 cases in 60,000 deliveries in his Vienna clinic; Eastman[2] stated that a complete placenta accreta had not been seen in 70,000 deliveries at Johns Hopkins. At St. Mary's Hospital in San Francisco, I found 3 cases of placenta accreta in 18,053 deliveries between Jan. 1, 1947, and Dec. 31, 1955; one of these was associated with a central placenta previa, and will be presented in detail. Until 1937, only 13 cases of placenta previa accreta had been reported; Irving and Hertig then added the fourteenth. Between 1942 and 1948, 7 additional cases were reported.[1, 3, 7, 15-17, 20] In 1952, Kistner, Hertig, and Reid[9] added 9 cases which had occurred at the Boston Lying-in Hospital during the preceding 15 years. Since 1952, the literature contains reports of 10 more cases.[4, 6, 8, 11, 13, 18, 19] Of these cases, only 4 or 5 were associated with central placenta previa.

Etiology.—The basic etiological factor, as in all cases of placenta accreta, is a decidual deficiency. It has been suggested by Kistner, Hertig, and Reid[9] that a larger percentage of cases of placenta previa would show some degree of placenta accreta if routine microscopic examinations of these placentas were performed.

Mrs. A. L., a 42-year-old gravida xi, para viii, who had had 2 abortions, was first seen in the Out Patient Department of St. Mary's Hospital in June, 1950. Her expected date of confinement was Nov. 1, 1950. Her first 7 deliveries were normal; the eighth delivery was by cesarean section because of a central placenta previa. Physical examination and routine laboratory tests were normal. The method of delivery was to be determined at term, but because of her parity vaginal delivery was expected. She had some spotting in July, 1950, and was hospitalized on Aug. 25, 1950, because of a considerable amount of "bright red vaginal bleeding"; this ceased almost immediately with bed rest and sedation, and she was dismissed without determination of the cause of the bleeding. At 5:00 A.M., on Sept. 7, 1950, she stated, she "passed a cupful of bright red blood vaginally." She entered St. Mary's Hospital at 6:20 A.M. but the bleeding had stopped. Blood was cross-matched and held available for transfusion. She began to bleed again, this time

profusely, at 10:00 A.M. Sterile vaginal examination disclosed the cervix to be thick, soft, and 2 to 3 cm. dilated. The placenta could be palpated covering the entire os. A diagnosis of central placenta previa was made and she was prepared for cesarean section. Fetal heart tones were audible and good.

At 11:35 A.M., cesarean section was begun under local infiltration which was later supplemented with a nitrous oxide-oxygen-ether mixture. The abdomen was opened in the midline. The lower uterine segment was found to be a very dark blue in color and resembled the fetal surface of a placenta with its engorged tortuous blood vessels. These vessels extended over the surface of the bladder and into the broad ligaments. Because of this exceptional vascularity, a classical type cesarean section was performed. A 4 pound female child was extracted from the right occipitoposterior position; its condition was poor and it subsequently died of atelectasis and prematurity. Attempt at removal of the placenta failed to show a line of cleavage. In what is now recognized as an overzealous and foolhardy attempt at its removal much of the placenta was manually torn from the uterine wall and the patient began to hemorrhage from the opened sinuses. That part of the placenta which lay over the cervix remained densely adherent and could not be separated. It was diagnosed as probable central placenta previa accreta and a total hysterectomy planned. This was performed with great difficulty due to the vascularity of the uterus and surrounding structures. The bladder was opened inadvertently and immediately closed. The patient went into profound shock for which she received 7 pints of blood and 2 units of plasma.



Fig. 1.—Section showing myometrial invasion by trophoblast. (×125; reduced ⅙.)

Postoperative care consisted of intravenous fluids, sedatives, and penicillin. A retention catheter was kept in the bladder for 5 days. Recovery was spectacular; she was ambulatory on the fifth and dismissed from the hospital on the eighth postoperative day.

Pathological Report.—The specimen consisted of a torn uterus with a considerable amount of adherent placenta, some detached placenta, a tube, and an ovary. Microscopic examination of the uterus showed myometrial invasion by the chorionic villi. The specimen was too damaged to obtain representative tissue from the cervix (Fig. 1).

Comment

One is reminded of the veracity of Mathieu's[12] statement, "Fortunate indeed is the one who finds placenta accreta at cesarean section rather than following vaginal delivery." Manual removal is too formidable a procedure, and one which should be condemned despite the attempt in this case. Phaneuf[14] found the maternal mortality to be 72 per cent following vaginal delivery and manual extraction of the placenta; 36.3 per cent with vaginal delivery and vaginal hysterectomy; 5.8 per cent with vaginal delivery and abdominal hysterectomy; and zero mortality following cesarean section and supravaginal hysterectomy. In this case, because of the location of the placenta, supravaginal hysterectomy was impossible. Perhaps, in view of the present definite trend toward total rather than supravaginal hysterectomy for other conditions, total hysterectomy should be the procedure of choice in placenta accreta if the patient's condition permits. Multiple blood transfusions and antibiotics have certainly lowered the maternal risk in recent years.

Summary

This is a previously unreported case of central placenta previa accreta. Treatment consisted of cesarean section and total hysterectomy. The pertinent literature is briefly reviewed.

References

1. Chisholm, W. N.: J. Obst. & Gynaec. Brit. Emp. **55**: 470, 1948.
2. Eastman, N. J.: Obst. & Gynec. Surv. **5**: 841, 1950.
3. Gemmell, A. A.: J. Obst. & Gynaec. Brit. Emp. **54**: 213, 1947.
4. Gomez Villalva, J. de D.: Rev. españ. obst. y. ginec. **12**: 161, 1953.
5. Irving, F. C., and Hertig, A. T.: Surg., Gynec. & Obst. **64**: 178, 1937.
6. Israel, S. L., Siegel, A., and Rubenstone, A.: Obst. & Gynec. **5**: 27, 1955.
7. Jackson, I.: Proc. Roy. Soc. Med. **36**: 362, 1945.
8. Keller, R., and Keller, B.: Bull. Féd. soc. gynec. et obst. **4**: 767, 1952.
9. Kistner, R. W., Hertig, A. T., and Reid, D. E.: Surg., Gynec. & Obst. **94**: 141, 1952.
10. Kraul, L.: Zentralbl. Gynäk. **52**: 828, 1928.
11. Lindner, A. J. J. M.: Nederl. tijdschr. geneesk. **97**: 1003, 1953.
12. Mathieu, A.: AM. J. OBST. & GYNEC. **33**: 498, 1937.
13. Parks, J., Barter, R. H., and Hill, R. P.: Obst. & Gynec. **2**: 391, 1953.
14. Phaneuf, L.: Surg., Gynec. & Obst. **57**: 343, 1933.
15. Rivière, M., and Chastrusse, M.: J. méd. Bordeaux **24**: 387, 1947.
16. Shannon, W. F., and Dodenhoff, C. F.: AM. J. OBST. & GYNEC. **53**: 326, 1947.
17. Shotton, D. M., and Taylor, C. W.: J. Obst. & Gynaec. Brit. Emp. **51**: 340, 1944.
18. Stone, M. L., Donnenfield, A. M., and Tanz, A.: AM. J. OBST. & GYNEC. **68**: 925, 1954.
19. Wachsman, D. V., and Moore, G. L.: Obst. & Gynec. **7**: 399, 1956.
20. Wilens, I.: Am. J. Surg. **58**: 434, 1942.

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CALCULATIONS IN ESTIMATING FETAL WEIGHT

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A METHOD for estimating fetal weight in utero with the use of McDonald's measurement (height of fundus with a tape measure) was published in September, 1954.[1] The standard deviation for this method was found to be 12.45 ounces (68 per cent within that range). Slightly over 50 per cent were within 8 ounces of the estimated weight.

The method is useful in private practice and in teaching medical students. Recently I have found a method of calculation which simplifies the procedure without changing the results obtained.

During the last trimester the presenting part is usually found at or below the pelvic brim. If it is not engaged, the estimated fetal weight is obtained by subtracting 13 from McDonald's measurement and multiplying by 0.34. If it is engaged, station zero, subtract 12 and multiply by 0.34. Since multiplication by 0.34 is nearly the same as division by 3, we have commonly used this easier procedure. Thus the formula for estimation of fetal weight may be expressed:

$$\frac{\text{McDonald's} - 13}{3} = \text{fetal weight in pounds.}$$

Or, if the presenting part is at station zero:

$$\frac{\text{McDonald's} - 12}{3} = \text{fetal weight in pounds.}$$

At a plus station, calculations are as follows:

$$\frac{\text{McDonald's} - 11}{3} = \text{fetal weight in pounds.}$$

Direct estimations in grams rather than pounds may be obtained by multiplying by 155 rather than by 0.34, Thus:

$$(\text{McDonald's} - 13)\ (155) = \text{fetal weight in grams.}$$

Correction for obesity, weight over 200 pounds, is done by subtracting 1 more from McDonald's measurement before multiplying or dividing.

The following example may clarify the procedure:

Height of fundus, 34 cm. Station, not engaged.

$$\frac{34 - 13}{3} = 7 \text{ pounds; or } 34 - 13 = 21 \times 0.34 = 7.14 \text{ pounds.}$$

$$34 - 13 = 21 \times 155 = 3{,}255 \text{ grams.}$$

Summary

Further simplification of calculations necessary in estimating fetal weight in utero is presented.

Reference

1. Johnson, R. W., and Toshach, C. E.: AM. J. OBST. & GYNEC. 68: 891, 1954.

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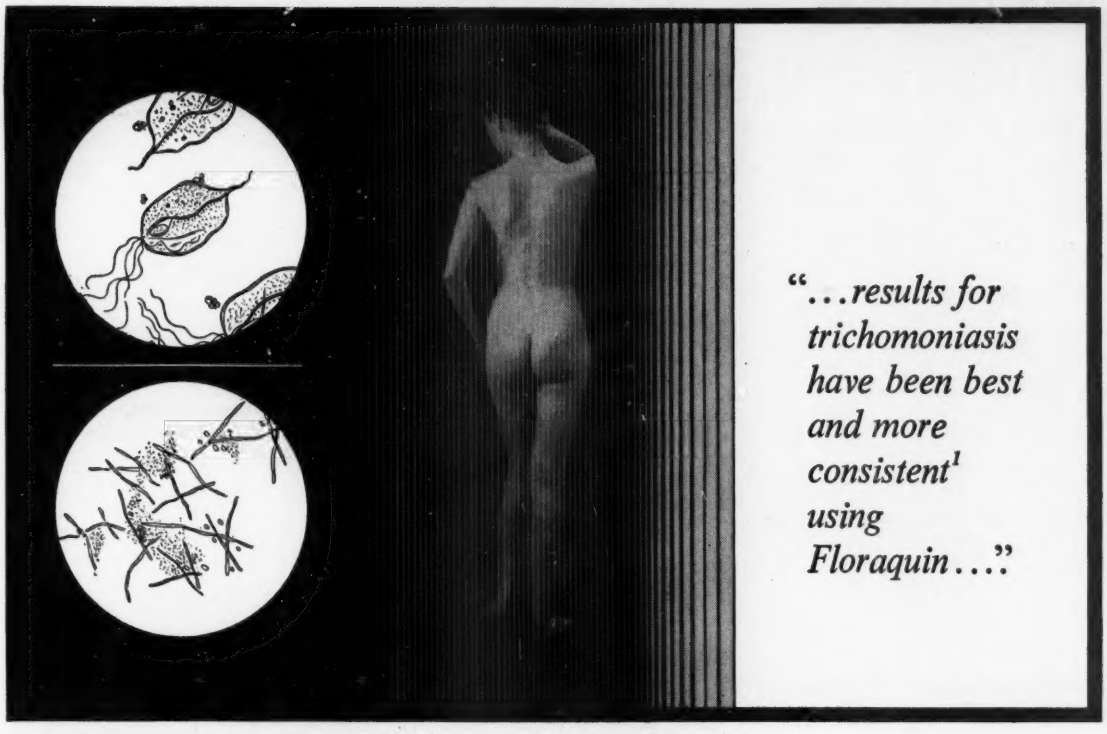
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It is with deep sorrow that we announce the sudden death on August 15 of Dr. William J. Dieckmann, Editor of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

Dr. Dieckmann's wide interest in the problems of obstetrics and gynecology, his careful attention to the details of publishing the JOURNAL, and his kindly cooperation will be missed by all who worked with him.

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1. Pitt, M. B.: Leukorrhea. Causes and Management, J. M. A. Alabama *25*:182 (Feb.) 1956.
2. Parker, R. T.; Jones, C. P., and Thomas, W. L.: Pruritus Vulvae, North Carolina M. J. *16*:570 (Dec.) 1955.

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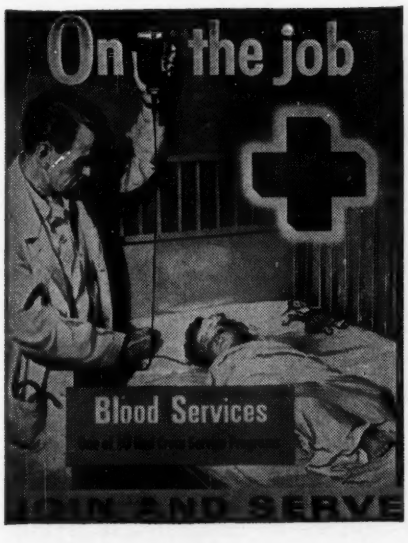
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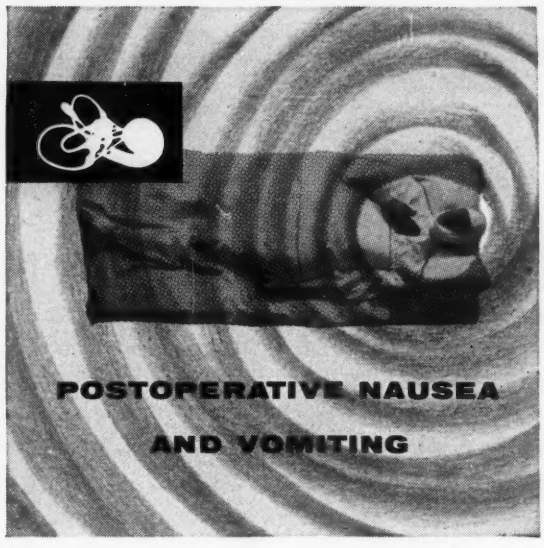
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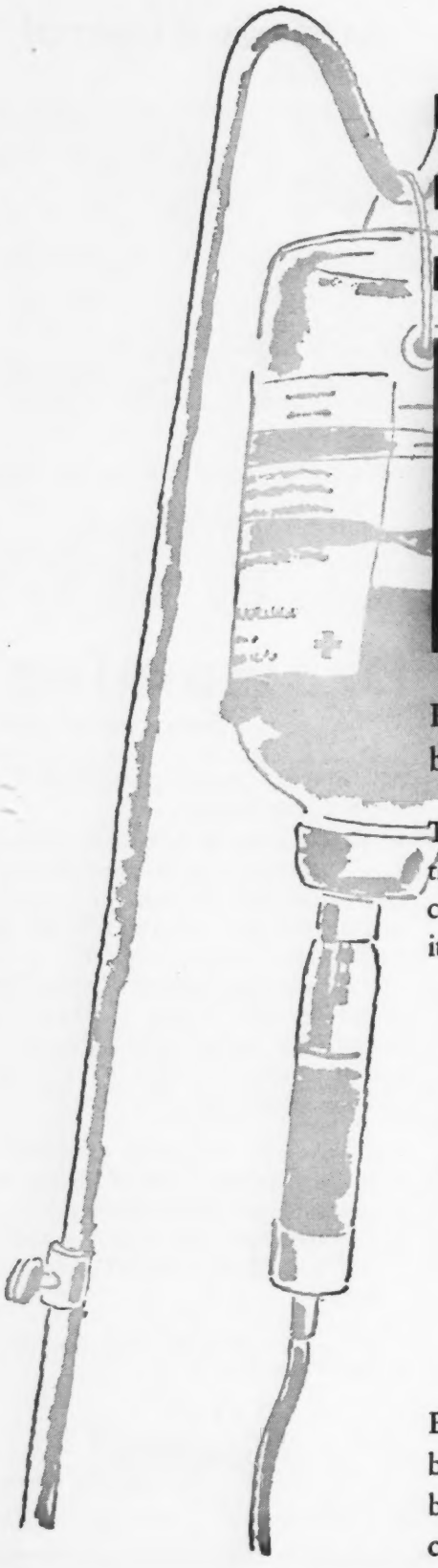
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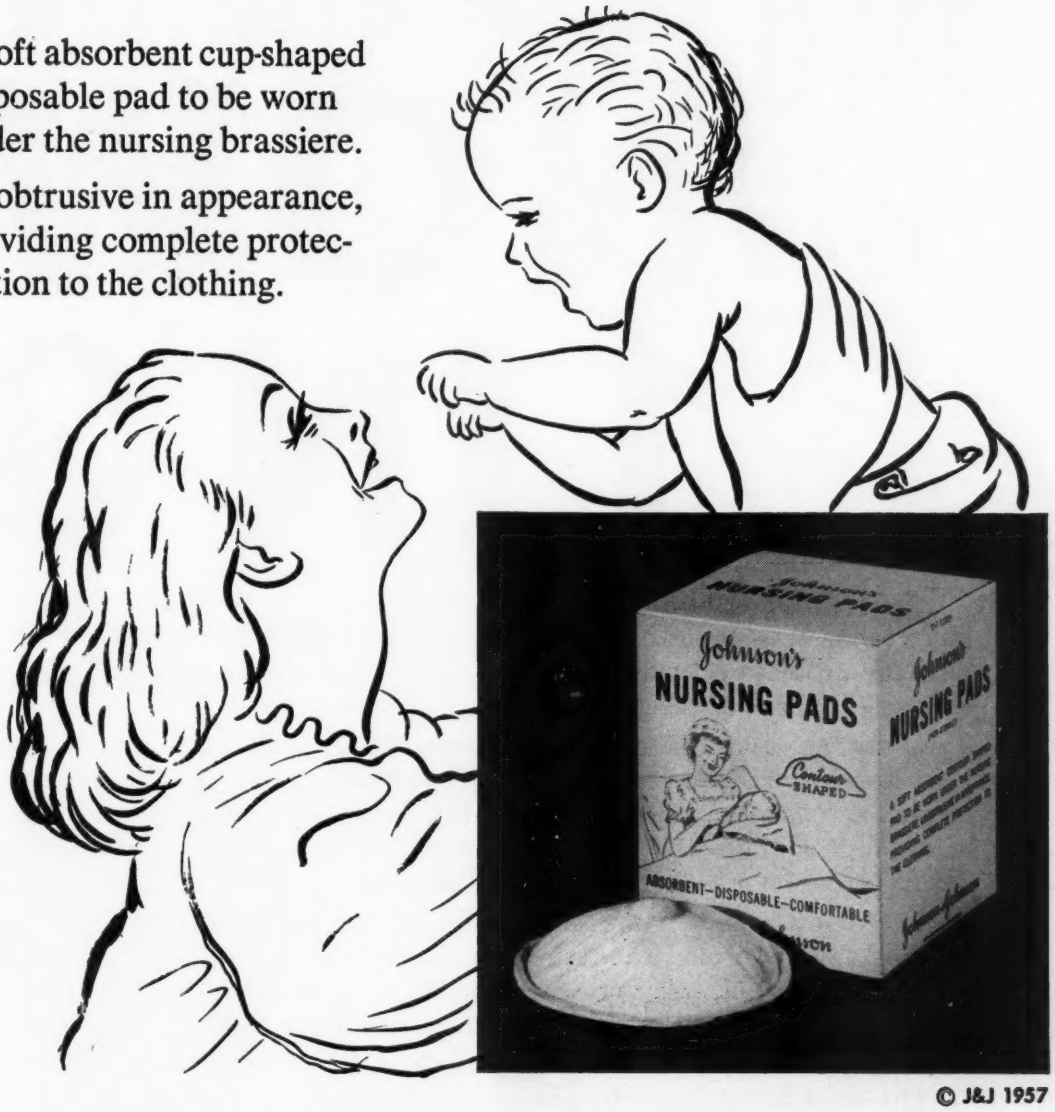
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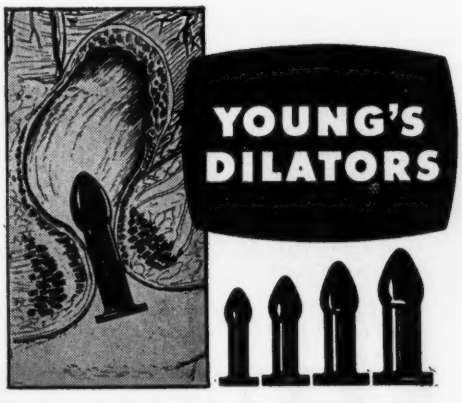
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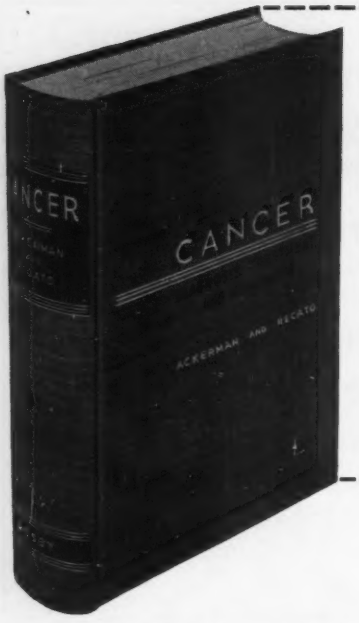
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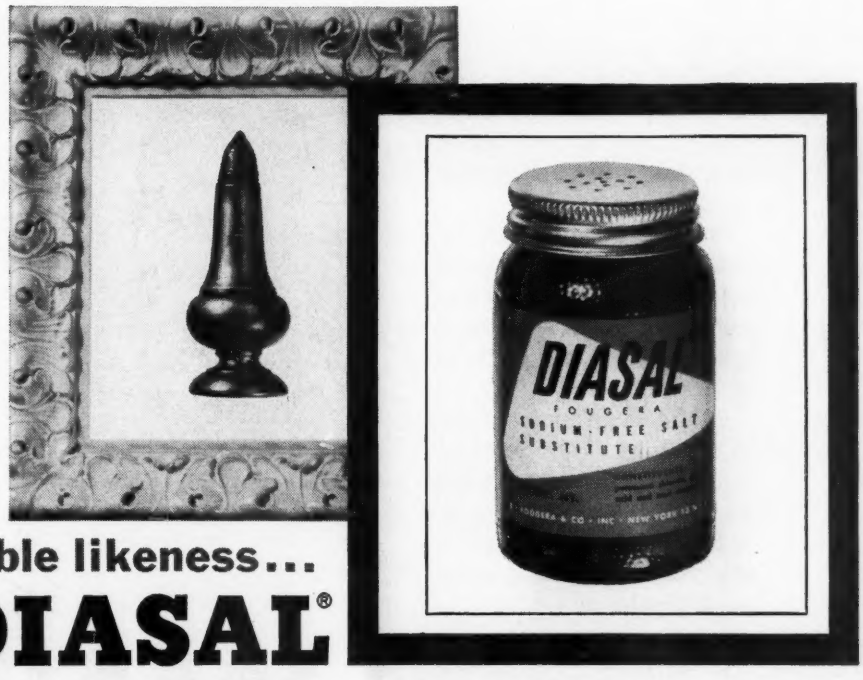
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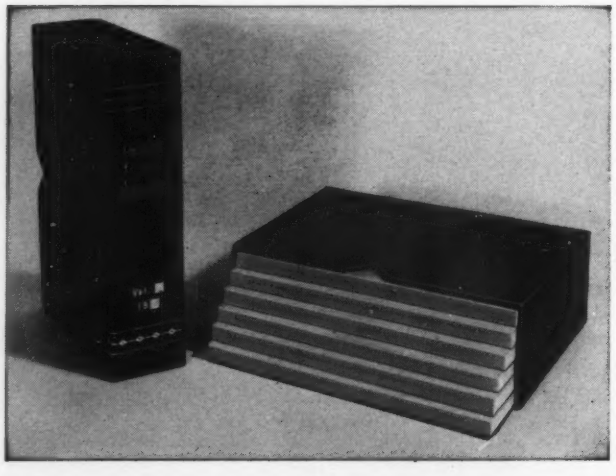
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adequate calcium for healthy, comfortable pregnancies

CALCIUM WITH PHOSPHORUS
for the patient whose diet has been low in phosphorus-rich foods, and should not be deprived of this mineral.

PHOSPHORUS-FREE CALCIUM
for the patient whose dietary phosphorus is relatively high, making additional phosphorus intake undesirable.



NOW.....WITH THERAPEUTIC B_6 AND FLAVINOL™

(hesperidin complex WALKER)

PRECALCIN® products recognize the need for adequate CALCIUM *intake during pregnancy.*

Walker LABORATORIES, INC., MOUNT VERNON, N. Y., U. S. A.

control nausea
and vomiting
of pregnancy
RECTALLY



ANTINAUSEA

SUPPRETTES®

- Provide prompt relief from nausea and vomiting
- One Supprette inserted rectally before arising usually suffices
- No refrigeration required—Supprettes can be kept at bedside
- No gastric upset
- Complete utilization of medication assured
- Synergistic combination of drugs enhances efficacy
- No discomfort, irritation or leak-back
- Helps pregnant women enjoy pregnancy

Supplied:
Antinausea Supprettes

No. 1 (pyrilamine maleate 50 mg., pentobarbital sodium ¾ gr.).

No. 2 (pyrilamine maleate 50 mg., pentobarbital sodium 1½ gr.).

In jars of 12.

The "Neocera" Base Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. Mixes readily with rectal fluids.

*Trademark U.C.C.

SUPPRETTE/SUCCESSOR TO THE SUPPOSITORY

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nutritionally complete . . . physiologic
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avoids excoriated buttocks
• minimizes digestive upsets
• virtually eliminates hyperirritability
due to subclinical tetany
• avoids excessive renal solute load,
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1 level measure to 2 fl.oz. hot water

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*parents of babies fed BREMIL are naturally tranquil, too